

第 12 期 pES club EBM 実践大会

平成 25 年 12 月 15 日
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<http://spell.umin.jp>

目標：GRADE system を理解し，個々の論文から Summary of Findings table と GRADE evidence profile を作成することができる。

課題：あなたは診療ガイドライン作成委員である。以下の 4 つのクリニカルクエスチョンのうち 1 つを選び，家のグループのメンバーと協力して，GRADE system に従い，GRADE profiler を用いて，Summary of Findings table と GRADE evidence profile を作りなさい。実践大会当日は，その作成手順について発表を行う。

注) GRADE profiler とは，GRADE working group が無償で提供している診療ガイドライン作成ソフトである。GRADE working group のサイト (<http://ims.cochrane.org/revman/other-resources/gradepro/download>) からダウンロード・インストールした上で作業する。

クリニカルクエスチョン：

1. COPD 患者は抗菌薬の予防投与を行うべきか (1COPD_ProphylacticABx) .
2. 小児の下痢にプロバイオティクスを使用するべきか (2ChildrenDierreha_Proviotics)
3. 糖尿病性足感染は通常治療に G-CSF を加えた方がいいか。 (3DiabeticFootInfection_G-CSF)
4. 急性心筋梗塞を起こした患者は酸素を吸入した方がいいか。 (4AMI_Oxgen)

進め方：

- ①家ごとに，他の家と重なることのないように，4 つのテーマのうち 1 つを選ぶ。
- ②Google site 上に，クリニカルクエスチョンごとのフォルダが作成されている。各フォルダには，クリニカルクエスチョン (PICO で示したものの，RevMan を用いて作成した Forest plot と Funnel plot 付き)，PICO に従って検索した結果集められた原著論文，原著論文をもとに作成されたデータ入力済み RevMan ファイルが入っている。

注) RevMan (Review Manager) とは，Cochrane Collaboration が無償で提供しているシステムティックレビューの作成ソフト (<http://ims.cochrane.org/revman>) である。

- ③3 ページ以降の手順に従い，インストールした GRADE profiler を用いて，家ごとに選んだクリニカルクエスチョンの RevMan ファイルを import する。家のメンバーで相談しアウトカムごとにバイアスの評価 (Downgrade/Upgrade) を行い，その結果を入力した上で，Summary of Findings table と GRADE evidence profile を作成する。
- ④完成した Summary of Findings table (ファイル名：“SoF_家の名前”) と GRADE evidence profile (ファイル名：“GRADE_EP_家の名前”) を南郷にメールで提出する。
- ⑤12 月 10 日 (火) に一度，進捗状況を南郷に報告すること。

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GRADE system についての詳細な解説は、以下のスライドを参考にするとよい。

http://homepage3.nifty.com/aihara/how_to_use_grade_aihara_20120426.ppt

特に、Downgrade/Upgradeについては、スライド 33~69 で解説されている。
作業に必要な Grade profiler の使用法は、以下の url に説明がある。

<http://homepage3.nifty.com/aihara/GRADEproHelp.html>

Risk of bias の bias 項目にはいくつかのバージョンがあるが、本課題では以下の項目で評価する。

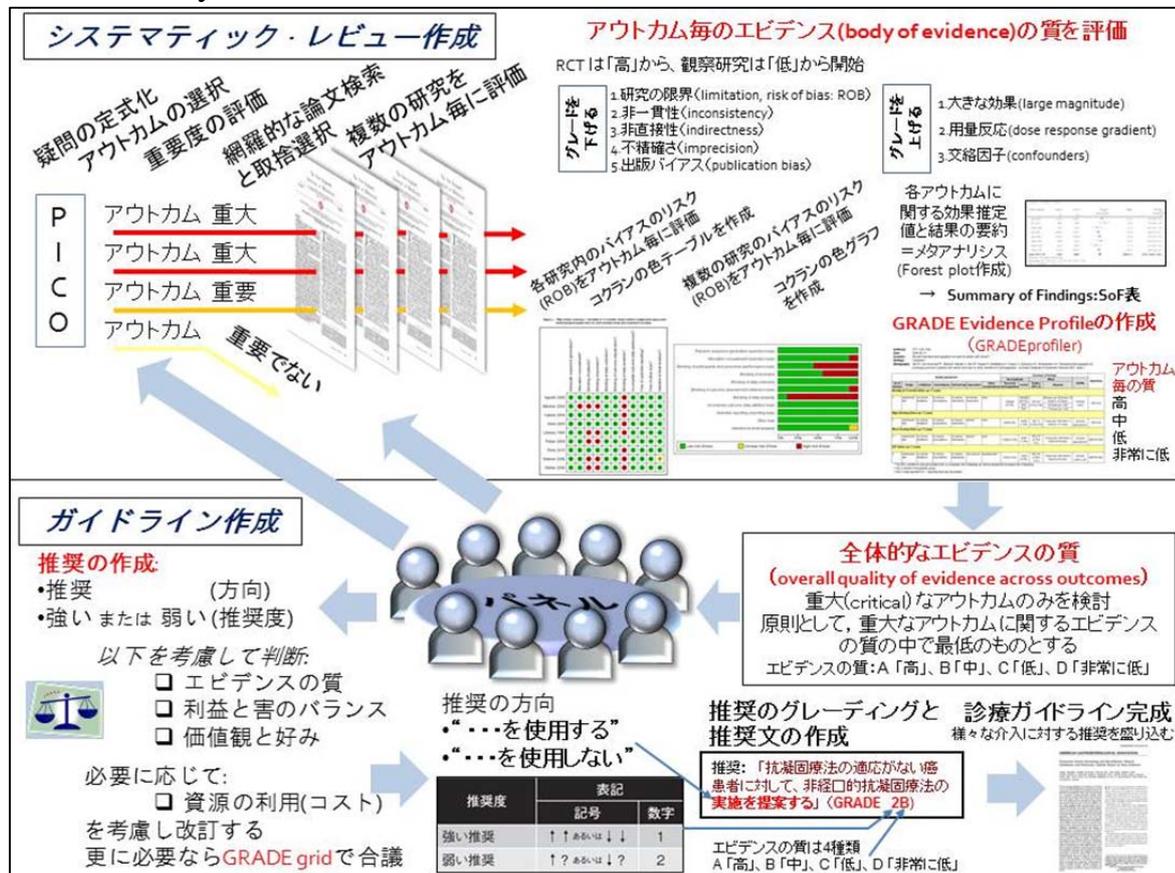
- | | |
|--|---------------------------------------|
| 1. Random sequence generation (selection bias) | 6. Blinding of outcome adjudicators? |
| 2. Allocation concealment (selection bias) | 7. Blinding of data analysts? |
| 3. Blinding of patients? | 8. Incomplete outcome data addressed? |
| 4. Blinding of providers? | 9. Free of selective reporting? |
| 5. Blinding of data collectors? | 10. Free of other bias? |
| | 11. Intention to treat analysis? |

Risk of bias の評価について、詳しくはコクランハンドブックの「Table 8.5.c: Criteria for judging risk of bias in the ‘Risk of bias’ assessment tool」を参照のこと。以下に説明がある。

http://hiv.cochrane.org/sites/hiv.cochrane.org/files/uploads/Ch08_Bias.pdf

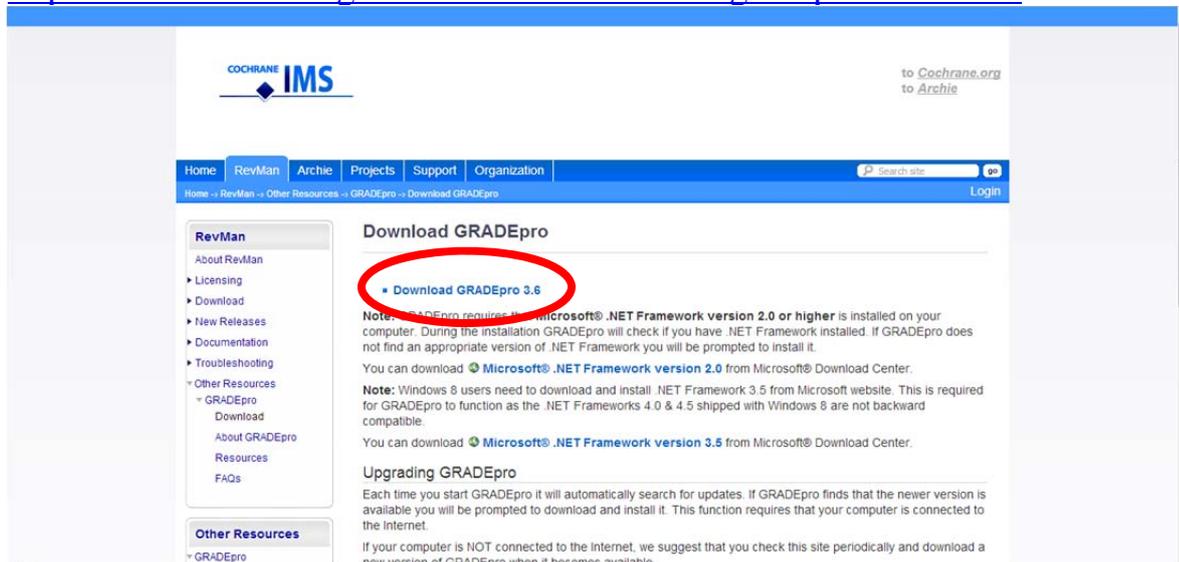
EBM 実践大会は、pES club で 1 年間 EBM を学んだ集大成となるものである。これまでに学んだこと全てを活用して取り組むこと。課題を進める上で不明な点、困ったことなどが生じた場合には、早めにメーリングリスト上か、南郷に直接質問すること。

【GRADE system 全体図】

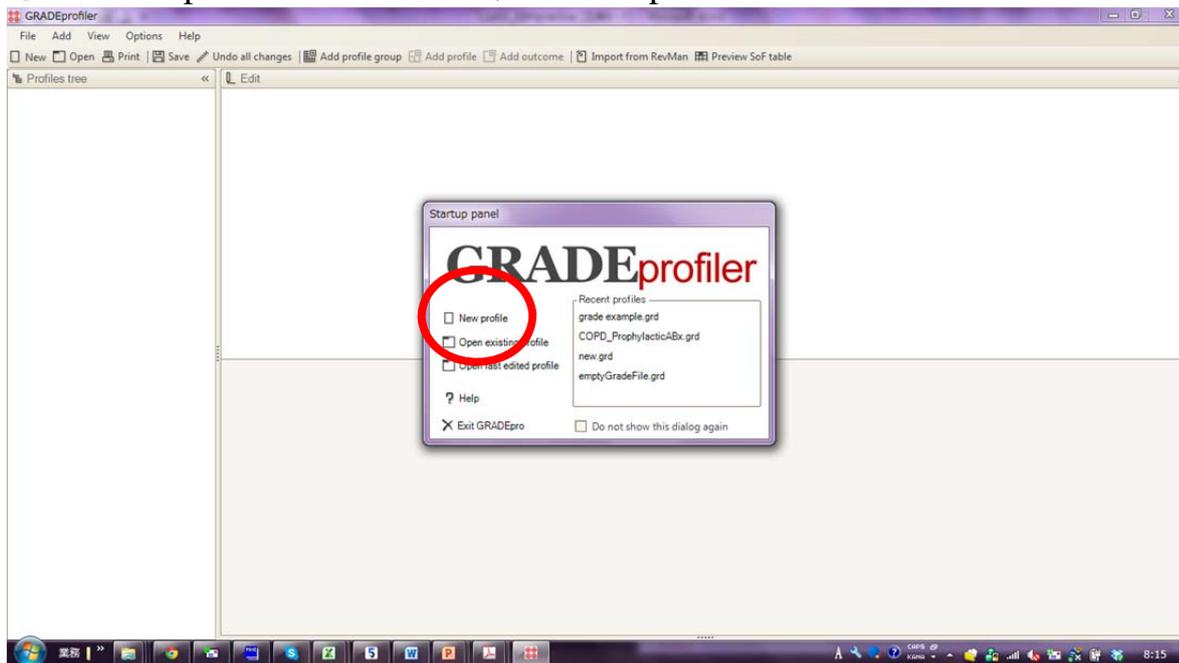


課題作成手順

①以下の url から GRADE profiler をダウンロードし、インストールする。
<http://ims.cochrane.org/revman/other-resources/gradepro/download>

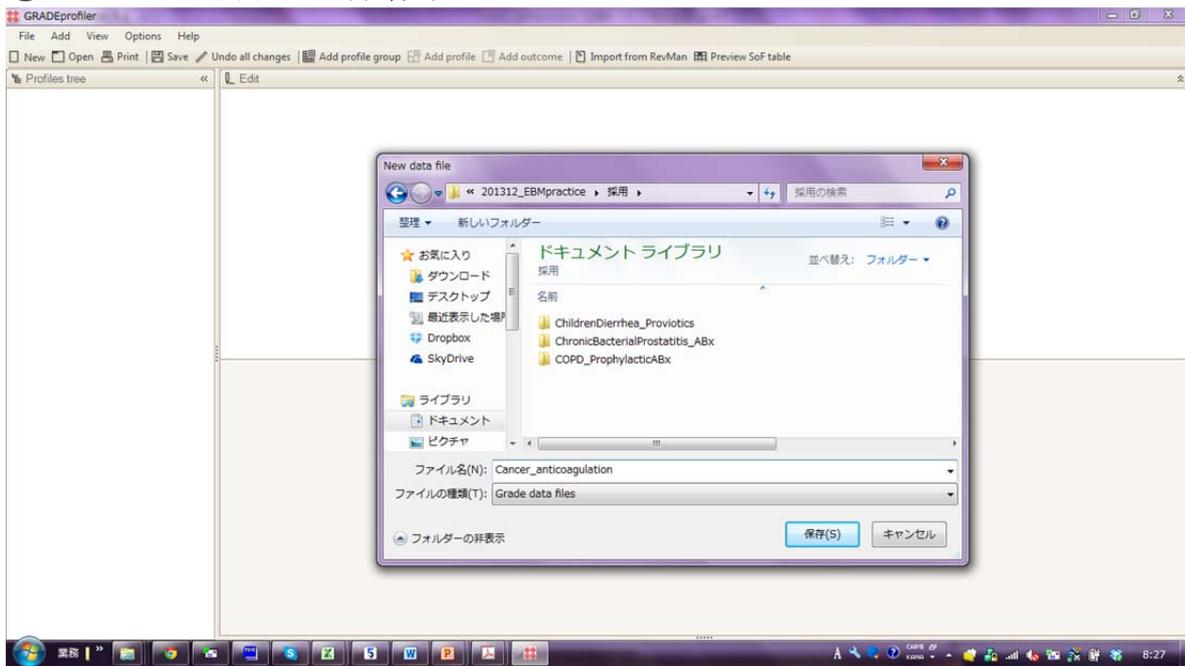


②GRADE profiler を開いたら，“New profile” をクリックする。

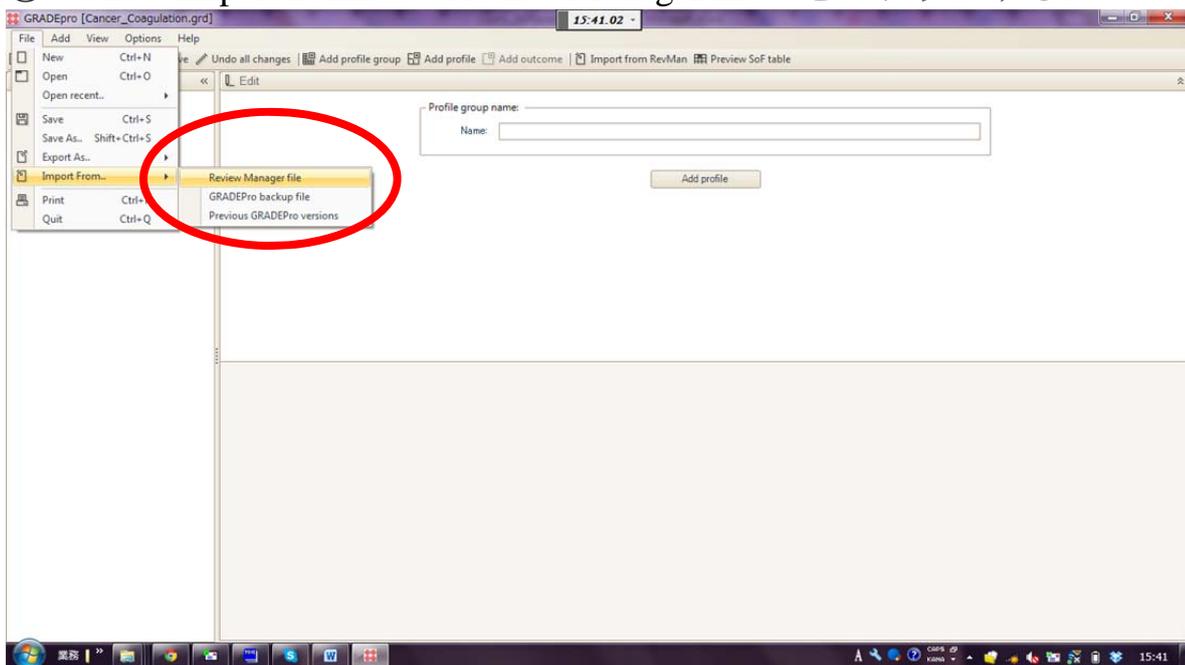


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③ タイトルを付けて保存する.

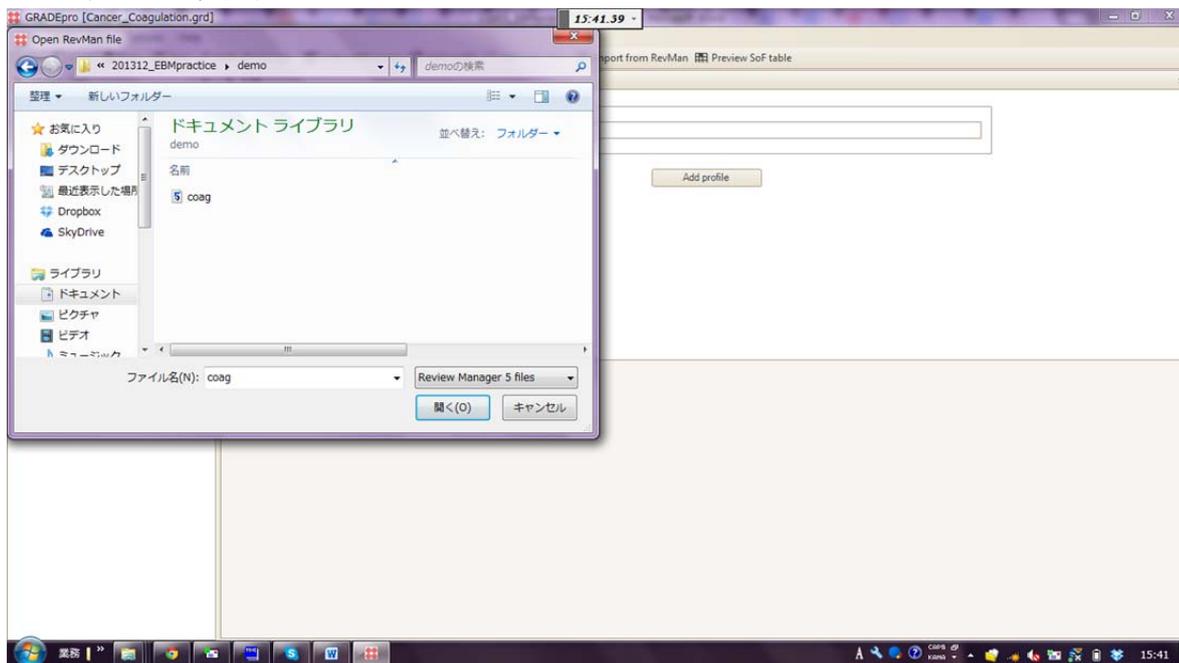


④ “File—Import Form...—Review Manager file” をクリックする.

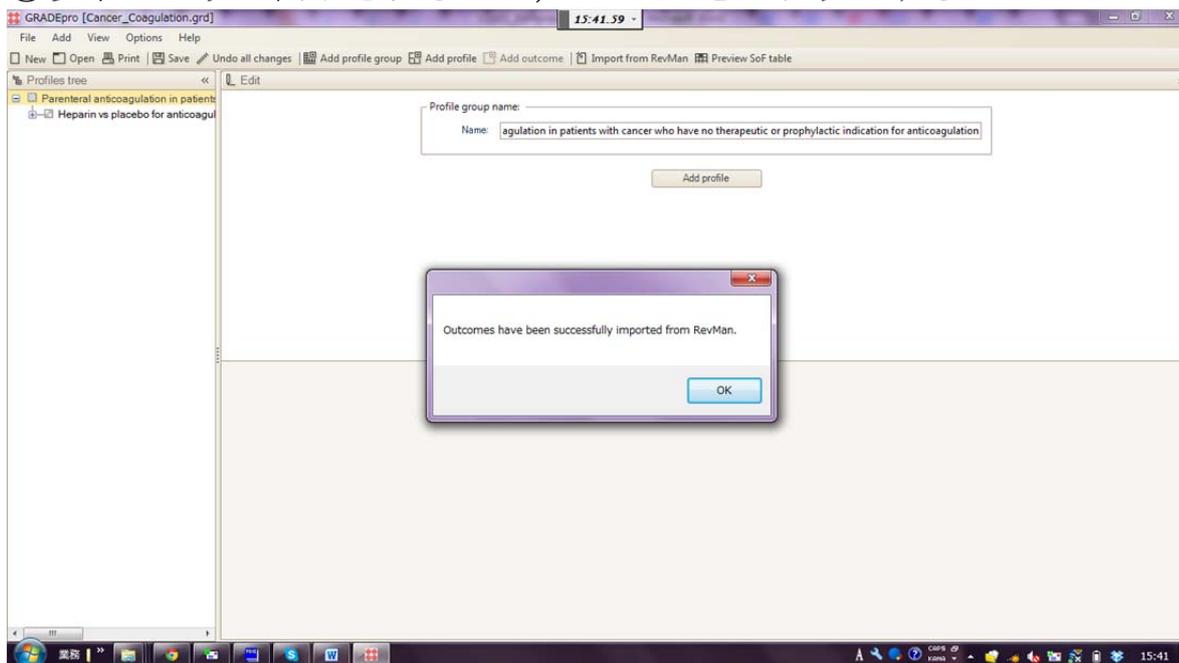


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⑤家で選んだクリニカルクエスチョンのフォルダにある Review Manager 5 file を選択して開く。



⑥以下のように表示されるので，“OK” をクリックする。



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⑦左カラムに表示された profile をクリックすると、右にその内容が表示される。

The screenshot shows the GRADEpro interface. On the left, the 'Profiles tree' has 'Parenteral anticoagulation in patients' expanded, with 'Heparin vs placebo for anticoagulation' selected and circled in red. The main area displays the 'Evidence profile' for this question: 'Should Heparin vs placebo be used for anticoagulation?'. The SoF title is 'Heparin compared to placebo for anticoagulation'. The format is 'Should [intervention] vs [comparison] be used for [health problem]'. The intervention is 'Heparin' and the comparison is 'placebo'. The health problem is 'anticoagulation'. The time frame is empty. Below this, the 'Profile information' section lists the authors and dates. The main table shows the profile for 'Mortality at 12 months | 8'. The table has columns for Design, Risk of bias, Inconsistency, Indirectness, Imprecision, Other considerations, and Importance. The design is 'no methodology chosen'. The table also shows patient and control characteristics, relative effect (RR 0.93), and absolute effects.

Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Importance
no methodology chosen					none	
Patients (Heparin) 735/1464 (50.2%)		Control (placebo) 594/1066 (55.7%)		Relative effect RR 0.93 (0.85 to 1.02)	Absolute effect 39 fewer per 1000 (from 84 fewer to 11 more)	Quality
		64.5%			45 fewer per 1000 (from 97 fewer to 13 more)	

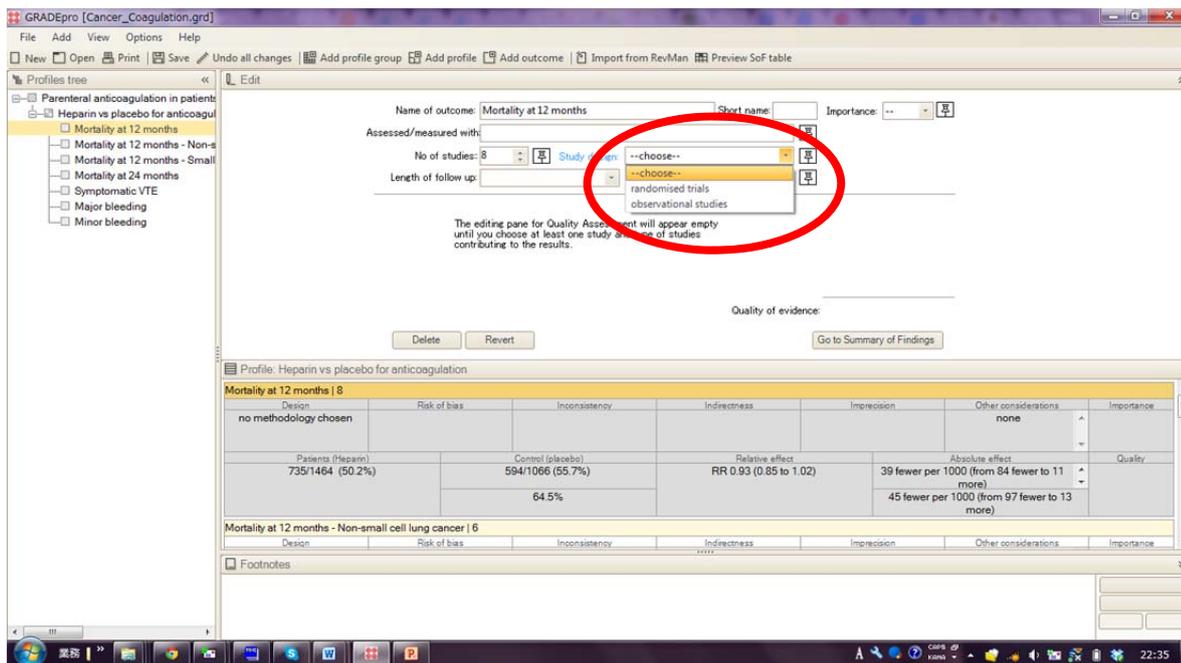
⑧Risk of Bias をクリックするとこのような表示になる。

The screenshot shows the GRADEpro interface with the 'Risk of Bias' assessment for the 'Mortality at 12 months' outcome. The left 'Profiles tree' has 'Mortality at 12 months' selected and circled in red. The main area shows the 'Editing pane for Quality Assessment' with fields for 'Name of outcome' (Mortality at 12 months), 'Assessed/measured with', 'No of studies' (8), and 'Study design'. Below this, the 'Quality of evidence' section is empty. The main table shows the profile for 'Mortality at 12 months | 8'. The 'Risk of bias' column is highlighted with a red circle, indicating it is the active assessment.

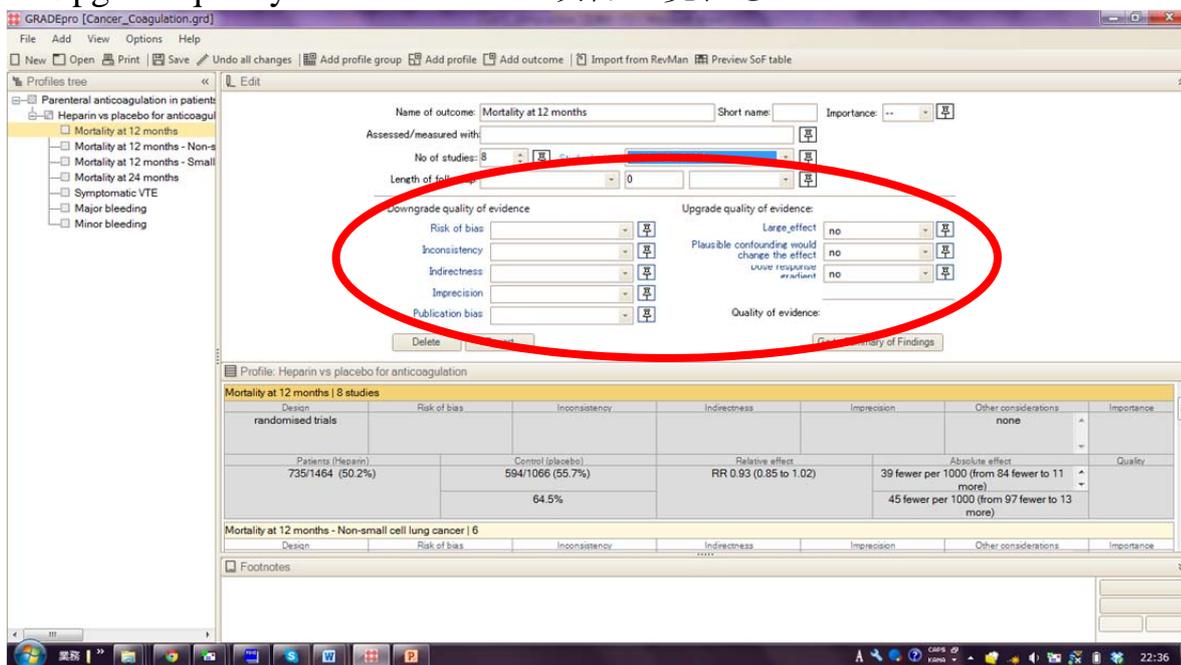
Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Importance
no methodology chosen					none	
Patients (Heparin) 735/1464 (50.2%)		Control (placebo) 594/1066 (55.7%)		Relative effect RR 0.93 (0.85 to 1.02)	Absolute effect 39 fewer per 1000 (from 84 fewer to 11 more)	Quality
		64.5%			45 fewer per 1000 (from 97 fewer to 13 more)	

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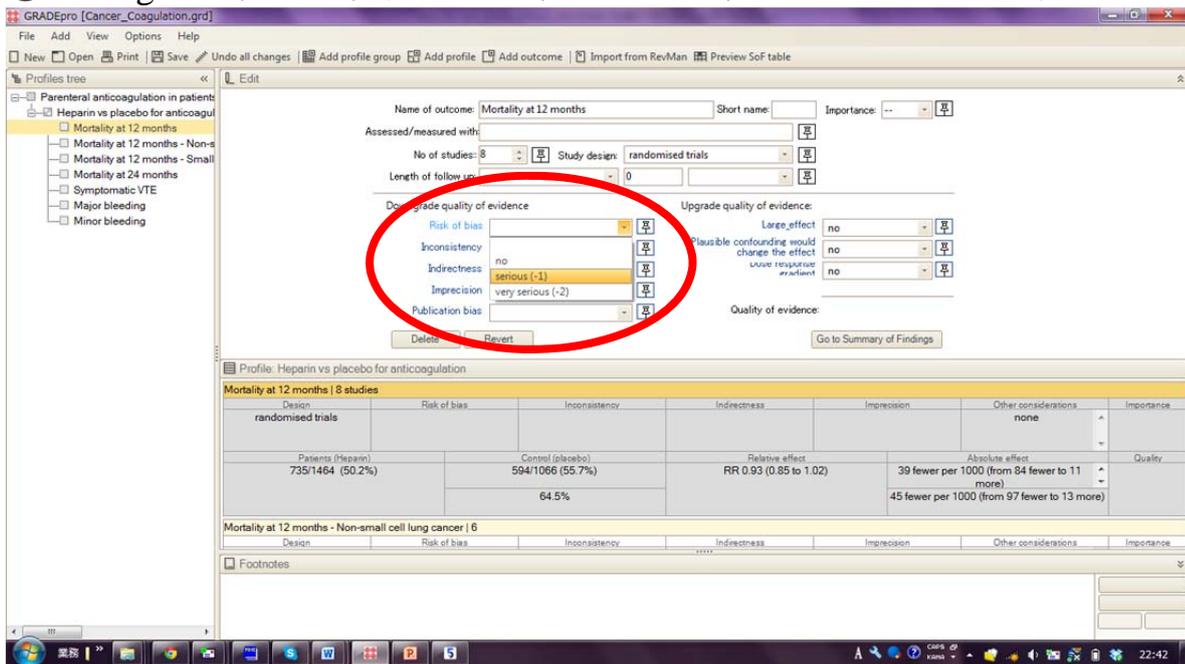
⑨上から 3 段目の “Study design” のところの “--choose--” をプルダウンして，“randomized trials” を選ぶ



⑩すると，1 番目の outcome についての，“Downgrade quality of evidence” と “Upgrade quality of evidence” の項目が現れる。

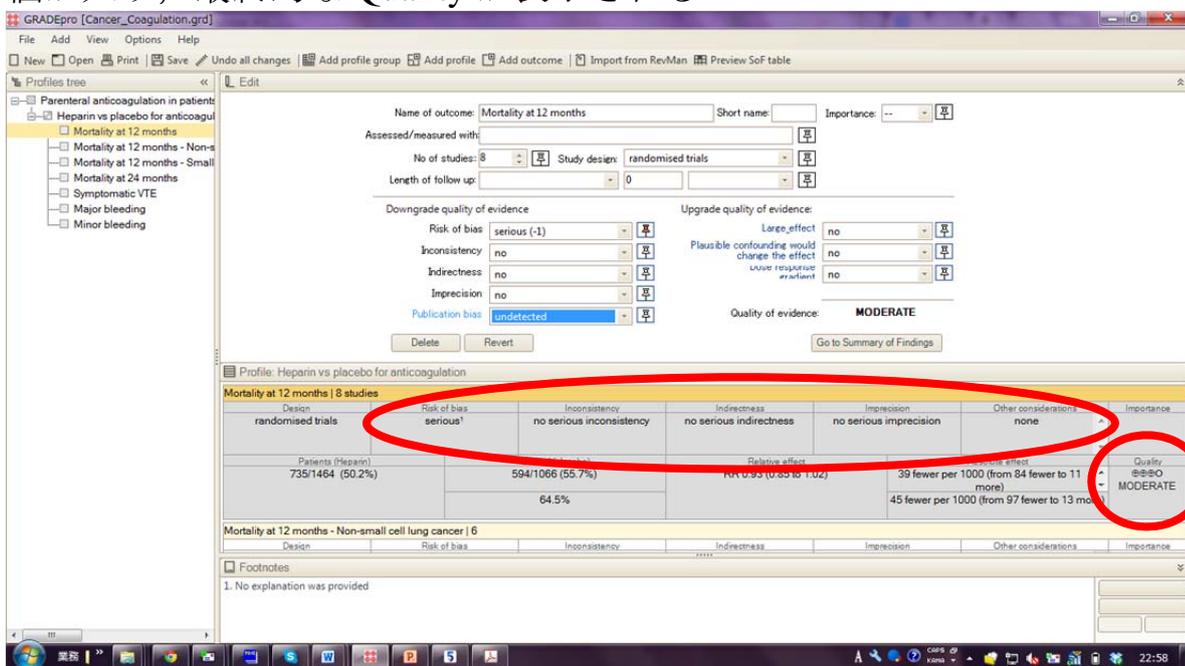


⑪ Downgrade する 5 項目を 1 つずつプルダウンして選んでいく。



“serious(-1)” や “very serious(-2)” を選ぶと、footnote にコメントを入力するのが義務であるとのアラートが表示されるが、本課題では無視して “Save” ボタンを押して先に進んで良い。

⑫ 全部選択し終わるとこのようになる。Profile の表に 5 項目の Downgrade の評価が入り、最終的な Quality が表示される。



以上で 1 つ目の outcome についての評価の入力が完了する。

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⑬2 つ目の outcome をクリックして，同様に Downgrade/Upgrade を入力していく．

GRADEpro [Cancer_Coagulation.grd]

File Add View Options Help

New Open Print Save Undo all changes Add profile group Add profile Add outcome Import from RevMan Preview SoF table

Profiles tree

- Parenteral anticoagulation in patients
 - Heparin vs placebo for anticoagulation
 - Mortality at 12 months
 - Mortality at 12 months - Non-small cell lung cancer (selected)
 - Mortality at 12 months - Small cell lung cancer
 - Mortality at 24 months
 - Major bleeding
 - Minor bleeding

Name of outcome: Mortality at 12 months - Non-small cell lung cancer Short name: Importance: --

Assessed/measured with:

No of studies: 6 Study design: randomised trials

Length of follow up: 0

Downgrade quality of evidence

Risk of bias: serious (-1) Inconsistency: no Indirectness: no Imprecision: no Publication bias: no

Upgrade quality of evidence

Large effect: no Plausible confounding would change the effect: no Value response gradient: no

Quality of evidence: MODERATE

Profile: Heparin vs placebo for anticoagulation

Mortality at 12 months 8 studies		Risk of bias		Inconsistency		Indirectness		Imprecision		Other considerations		Importance	
randomised trials		serious ¹		no serious inconsistency		no serious indirectness		no serious imprecision		none			
Patients (heparin)	735/1464 (50.2%)	Control (placebo)	594/1066 (55.7%)	RR 0.93 (0.85 to 1.02)		39 fewer per 1000 (from 84 fewer to 11 more)		45 fewer per 1000 (from 97 fewer to 13 more)				MODERATE	
		64.5%											

Footnotes

1. No explanation was provided

⑭全ての outcome について入力し終わったら，ツールバーにある“Preview SoF table”をクリックする．

GRADEpro [Cancer_Coagulation.grd]

File Add View Options Help

New Open Print Save Undo all changes Add profile group Add profile Add outcome Import from RevMan Preview SoF table

Profiles tree

- Parenteral anticoagulation in patients
 - Heparin vs placebo for anticoagulation
 - Mortality at 12 months
 - Mortality at 12 months - Non-small cell lung cancer
 - Mortality at 12 months - Small cell lung cancer
 - Mortality at 24 months
 - Symptomatic VTE
 - Major bleeding
 - Minor bleeding (selected)

Name of outcome: Minor bleeding Short name: Importance: --

Assessed/measured with:

No of studies: 7 Study design: randomised trials

Length of follow up: 0

Downgrade quality of evidence

Risk of bias: serious (-1) Inconsistency: no Indirectness: no Imprecision: no Publication bias: strongly suspected (+1)

Upgrade quality of evidence

Large effect: no Plausible confounding would change the effect: no Value response gradient: no

Quality of evidence: LOW

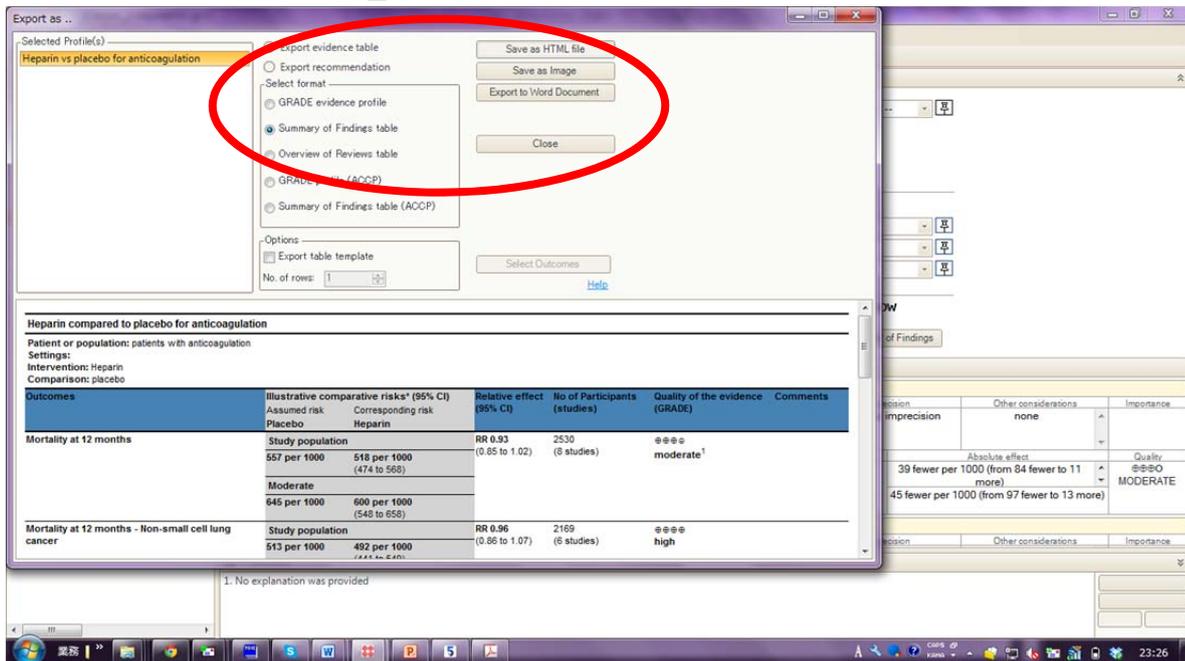
Profile: Heparin vs placebo for anticoagulation

Mortality at 12 months 8 studies		Risk of bias		Inconsistency		Indirectness		Imprecision		Other considerations		Importance	
randomised trials		serious ¹		no serious inconsistency		no serious indirectness		no serious imprecision		none			
Patients (heparin)	735/1464 (50.2%)	Control (placebo)	594/1066 (55.7%)	RR 0.93 (0.85 to 1.02)		39 fewer per 1000 (from 84 fewer to 11 more)		45 fewer per 1000 (from 97 fewer to 13 more)				MODERATE	
		64.5%											

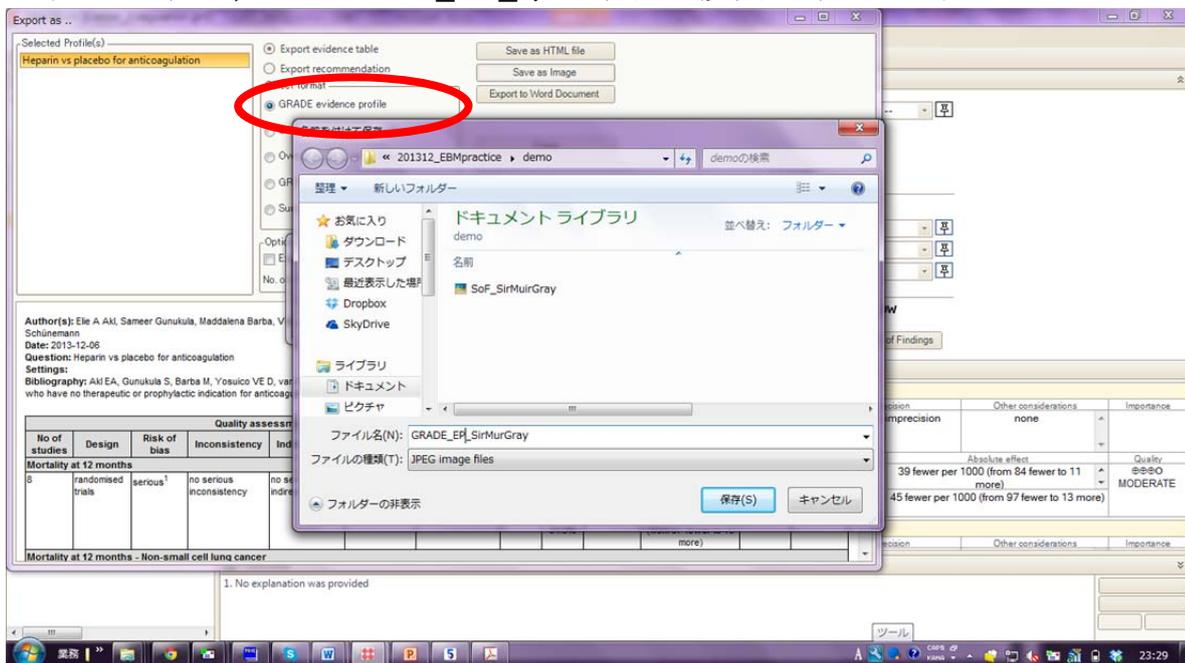
Footnotes

1. No explanation was provided

⑮ “Export as” の “Summary of Findings table” を “Save as Image” で保存する。ファイル名は，“SoF_家の名前（英語で）” とすること。



⑯続いて，“GRADE evidence profile” も同様に “Save as Image” で保存する。ファイル名は，“GRADE_EP_家の名前（英語で）” とすること。



Summary of Findings table（ファイル名：“SoF_家の名前”）と GRADE evidence profile（ファイル名：“GRADE_EP_家の名前”）を南郷に提出する。

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Summary of Findings table とは， 以下のような表である。

Heparin compared to placebo for anticoagulation						
Patient or population: patients with anticoagulation						
Settings:						
Intervention: Heparin						
Comparison: placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Placebo	Corresponding risk Heparin				
Mortality at 12 months	Study population		RR 0.93 (0.85 to 1.02)	2530 (8 studies)	⊕⊕⊕⊕ moderate ¹	
	557 per 1000	518 per 1000 (474 to 568)				
	Moderate					
	645 per 1000	600 per 1000 (548 to 658)				
Mortality at 12 months - Non-small cell lung cancer	Study population		RR 0.96 (0.86 to 1.07)	2169 (6 studies)	⊕⊕⊕⊕ high	
	513 per 1000	492 per 1000 (441 to 549)				
	Moderate					
	593 per 1000	569 per 1000 (510 to 635)				
Mortality at 12 months - Small cell lung cancer	Study population		RR 0.86 (0.75 to 0.98)	361 (2 studies)	⊕⊕⊕⊕ low ¹	
	773 per 1000	665 per 1000 (580 to 758)				
	Moderate					
	753 per 1000	648 per 1000 (565 to 738)				
Mortality at 24 months	Study population		RR 0.92 (0.88 to 0.97)	1174 (5 studies)	⊕⊕⊕⊕ high	
	859 per 1000	790 per 1000 (756 to 833)				
	Moderate					
	831 per 1000	765 per 1000 (731 to 806)				
Symptomatic VTE	Study population		RR 0.55 (0.37 to 0.82)	2264 (7 studies)	⊕⊕⊕⊕ moderate ¹	
	62 per 1000	34 per 1000 (23 to 50)				
	Moderate					
	29 per 1000	16 per 1000 (11 to 24)				
Major bleeding	Study population		RR 1.3 (0.59 to 2.88)	2843 (9 studies)	⊕⊕⊕⊕ very low ¹	
	19 per 1000	25 per 1000 (11 to 54)				
	Moderate					
	7 per 1000	9 per 1000 (4 to 20)				
Minor bleeding	Study population		RR 1.05 (0.75 to 1.46)	2345 (7 studies)	⊕⊕⊕⊕ low ¹	
	51 per 1000	54 per 1000 (38 to 74)				
	Moderate					
	27 per 1000	28 per 1000 (20 to 39)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ No explanation was provided

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GRADE evidence profile とは、以下のような表である。

Author(s): Elie A Akl, Sameer Gunukula, Maddalena Barba, Victor E D Yosucio, Frederiek F van Doormaal, Saskia Kuipers, Saskia Middeldorp, Heather O Dickinson, Andrew Bryant, Holger Schünemann

Date: 2013-12-06

Question: Heparin vs placebo for anticoagulation

Settings:

Bibliography: Akl EA, Gunukula S, Barba M, Yosucio VE D, van Doormaal FF, Kuipers S, Middeldorp S, Dickinson HO, Bryant A, Schünemann H. Parenteral anticoagulation in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

No of studies	Design	Quality assessment					Other considerations	No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Heparin		Placebo	Relative (95% CI)	Absolute			
Mortality at 12 months													
8	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	735/1464 (50.2%)	594/1066 (55.7%)	RR 0.93 (0.85 to 1.02)	39 fewer per 1000 (from 84 fewer to 11 more)	⊕⊕⊕○ MODERATE		
								64.5%		45 fewer per 1000 (from 97 fewer to 13 more)			
Mortality at 12 months - Non-small cell lung cancer													
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	617/1284 (48.1%)	454/885 (51.3%)	RR 0.96 (0.86 to 1.07)	21 fewer per 1000 (from 72 fewer to 36 more)	⊕⊕⊕⊕ HIGH		
								59.3%		24 fewer per 1000 (from 83 fewer to 42 more)			
Mortality at 12 months - Small cell lung cancer													
2	randomised trials	serious ¹	serious ¹	no serious indirectness	no serious imprecision	none ¹	118/180 (65.6%)	140/181 (77.3%)	RR 0.86 (0.75 to 0.98)	108 fewer per 1000 (from 15 fewer to 193 fewer)	⊕⊕○○ LOW		
								75.3%		105 fewer per 1000 (from 15 fewer to 188 fewer)			
Mortality at 24 months													
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	461/586 (78.7%)	505/588 (85.9%)	RR 0.92 (0.88 to 0.97)	69 fewer per 1000 (from 26 fewer to 103 fewer)	⊕⊕⊕⊕ HIGH		
								83.1%		66 fewer per 1000 (from 25 fewer to 100 fewer)			
Symptomatic VTE													
7	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/1338 (2.8%)	57/926 (6.2%)	RR 0.55 (0.37 to 0.82)	28 fewer per 1000 (from 11 fewer to 39 fewer)	⊕⊕⊕○ MODERATE		
								2.9%		13 fewer per 1000 (from 5 fewer to 18 fewer)			
Major bleeding													
9	randomised trials	serious ¹	serious ¹	no serious indirectness	no serious imprecision	reporting bias ¹	30/1624 (1.8%)	23/1219 (1.9%)	RR 1.3 (0.59 to 2.88)	6 more per 1000 (from 8 fewer to 35 more)	○○○○ VERY LOW		
								0.7%		2 more per 1000 (from 3 fewer to 13 more)			
Minor bleeding													
7	randomised trials	serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias ¹	85/1365 (6.2%)	50/980 (5.1%)	RR 1.05 (0.75 to 1.46)	3 more per 1000 (from 13 fewer to 23 more)	⊕○○○ LOW		
								2.7%		1 more per 1000 (from 7 fewer to 12 more)			

¹ No explanation was provided