

Summary of Findings and Interpreting Reviews

Applicability and Recommendations
Methods Group

(schuneh@mcmaster.ca)

Disclosure

Relevant Financial Relationships

- Member of the GRADE working group: honoraria related to this work deposited into research accounts

Off label medication

- None mentioned

Content

- Rationale for Summary of Findings Tables (SoF) (Cochrane Handbook)
- Content of the SoF Tables
- Interpreting results (Cochrane Handbook)
- Research and future of SoF tables

Example (1)

Main results

Twenty RCTs met the inclusion criteria. Concomitant therapy varied from none to any other bronchodilator plus corticosteroid (oral and inhaled). The following outcomes were significantly different when compared to placebo.

Forced expiratory volume in one second (FEV1) improved with treatment: Weighted Mean Difference (WMD) 100 ml; 95% Confidence Interval (CI) 40 to 160 ml. Similarly for forced vital capacity (FVC): WMD 210 ml 95%CI 100 to 320. Two studies reported an improvement in maximum oxygen consumption (VO2 max); WMD 195 ml/min, 95%CI 113 to 278. At rest, arterial oxygen tension at rest (PaO2) and arterial carbon dioxide tension at rest (PaCO2) both improved with treatment (WMD 3.2 mm Hg; 95%CI 1.2 to 5.1, and WMD -2.4 mm Hg; 95%CI -3.5 to -1.2, respectively). Walking distance tests did not improve (four studies, Standardised Mean Difference 0.30, 95%CI -0.01 to 0.62), neither did Visual Analogue Score for breathlessness in two small studies (WMD 3.6, 95%CI -4.6 to 11.8). The Relative Risk (RR) of nausea was greater with theophylline (RR 7.7; 95%CI 1.5 to 39.9). However, patients' preference for theophylline was greater than that for placebo (RR 2.27; 95%CI 1.26 to 4.11). Very few participants withdrew from these studies for any reason.

Example (2)

Main results

From 459 titles 24 studies met the inclusion criteria. Treatment lasted three weeks or less in 19 studies, high dose oral steroid was used in 21 studies and subjects had moderate or severe COPD in 15 studies. There was a significant difference in FEV1 after two weeks treatment, WMD 53.30 ml; 95% confidence interval 22.21 to 84.39 favouring oral steroid use compared to placebo when 14 studies with available data (n=396) were combined, with no significant heterogeneity. There was a significant increase in odds for individual patient FEV1 response greater than 20% from baseline with high dose oral steroid treatment compared to placebo, OR 2.71; 95% CI 1.84 to 4.01 (9 studies) . It would be necessary to treat 7 patients (95% CI 5 to 12) with oral corticosteroids to achieve one extra case of increasing FEV1 by more than 20%, with a placebo group risk of 0.13. All differences in health-related quality of life were less than the minimum clinically important difference.

Authors' conclusions

There is no evidence to support the long-term use of oral steroids at doses less than 10-15 mg prednisolone though some evidence that higher doses (≥ 30 mg prednisolone) improve lung function over a short period. Potentially harmful adverse effects e.g., diabetes, hypertension, osteoporosis would prevent recommending long-term use at these high doses in most patients.

Background to SoF Tables

A brief presentation, discussion and conclusions about the following issues can help people make better informed decisions and increase the usability of Cochrane reviews:

- The quality of the evidence
- Information on all important outcomes
- The applicability of the results
- Other information, such as considerations of harms costs and current practice, that might be relevant to someone making a decision
- Clarification of the expected balance of benefits, harms, burden and costs of the intervention

SoF are supposed to present this information

Systematic reviews inform decision making and policy

- GRADE group – found no standardized way of presenting information from a systematic review in a summary format
- GRADE evidence profiles summarize what is known for a specific question to allow issuing guidance
- application in systematic reviews

Preliminary work

- revealed that users would appreciate a summary of the findings upfront to facilitate interpretation
- evaluated the type and amount of information users want
- e.g. number of outcomes ≤ 7
- presenting information on all important outcomes
- ordering of outcomes

Features of SoF Tables

- SoF table provides key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all important outcomes.
- Planning for the SoF table comes early in the systematic review, with the selection of the outcomes to be included in (i) the review and (ii) the SoF table.
- This has not typically been formally addressed in traditional Cochrane reviews.

General template for SoF

- i) a list of all important outcomes, both desirable and undesirable;
- (ii) numbers of participants and studies addressing these outcomes;
- (iii) a measure of the typical burden of these outcomes (e.g. the control group risk or control group mean);
- (iv) a measure of the magnitude of effect;
- (v) a rating of the overall quality of evidence (which may vary by outcome); and
- (vi) space for comments.

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)

Settings: International air travel

Intervention: Compression stockings¹

Comparison: Without stockings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Without stockings	Corresponding risk With stockings				
Symptomatic deep vein thrombosis (DVT)	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed symptomatic DVT in these studies.
Symptom-less deep vein thrombosis	Low risk population ² 10 per 1000		RR 0.10 (0.05 to 0.25)	2637 (9 studies)	⊕⊕⊕⊕ High	
	High risk population ² 30 per 1000					
Superficial vein thrombosis	13 per 1000	6 per 1000 (2 to 15)	RR 0.45 (0.18 to 1.13)	1804 (8 studies)	⊕⊕⊕○ Moderate ³	
Oedema Post-flight values. Scale from 0, no oedema, to 10, maximum oedema.	The mean oedema ranged across control groups from 6 to 9.	The mean oedema in the intervention groups was on average 4.7 lower (4.5 to 4.9 lower).		1246 (6 studies)	⊕⊕○○ Low ⁴	
Pulmonary embolus	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed pulmonary embolus in these studies.
Death	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants died in these studies.
Adverse effects	See comment	See comment	Not estimable	1182 (4 studies)	See comment	The tolerability of the stockings was described as very good with no complaints of side effects in 4 studies. ⁵

*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: Relative Risk

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 All the stockings in the 9 trials included in this review were below-knee compression stockings. In four trials the compression strength was 20-30 mm Hg at the ankle. It was 10-20 mm Hg in the other four trials. Stockings come in different sizes. If a stocking is too tight around the knee it can prevent essential venous return causing the blood to pool around the knee. Compression stockings should be fitted properly. A stocking that is too tight could cut into the skin on a long flight and potentially cause ulceration and increased risk of DVT. Some stockings can be slightly thicker than normal leg covering and can be potentially restrictive with tight foot wear. It is a good idea to wear stockings around the house prior to travel to ensure a good, comfortable fitting. Stockings were put on 2 to 3 hours before the flight in most of the trials. The availability and cost of stockings can vary.

² Two trials recruited high risk participants defined as those with previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous two years, large varicose veins or, in one of the studies, participants taller than 190 cm and heavier than 90 kg. The incidence for 7 trials that excluded high risk participants was 1.45% and the incidence for the 2 trials that recruited high-risk participants (with at least one risk factor) was 2.43%. We have rounded these off to 10 and 30 per 1,000 respectively.

³ The confidence interval crosses no difference and does not rule out a small increase.

⁴ The measurement of oedema was not validated or blinded to the intervention. All of these studies were conducted by the same investigators.

⁵ None of the other trials reported adverse effects, apart from 4 cases of superficial vein thrombosis in varicose veins in the knee region that were compressed by the upper edge of the stocking in one trial.

Pilot study of Cochrane review groups

- headed by Gunn Vist (Oslo)
- 17 Cochrane Review groups participated
- 20 review authors participated (20 new or updated reviews)
- spent an additional 4 hours (2 to 40 hours)

Results of first pilot

- layout clear
- generally found to be helpful
- 11/17 increased accessibility
- 5/17 improved quality
- 1/17 rephrased conclusions
- software difficulties

What exactly is in a SoF Table?

- Title
- Patients and population
- Setting

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)

Settings: International air travel

Intervention: Compression stockings¹

Comparison: Without stockings

Up to seven outcomes

Outcomes	Predicted Control group risk	Corresponding Absolute effect (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence	Comments
	Without stockings	With stockings				
Symptom-less deep vein thrombosis (DVT)	Low risk population		RR 0.10 (0.05 to 0.25)	2637 (9)	⊕⊕⊕⊕ High	In 3 trials with a total of 483 participants, 0 had symptom-less DVT.
	10 per 1000 ¹	9 fewer per 1000 (7 to 10)				
Symptom-less deep vein thrombosis (DVT)	High risk population					
	30 per 1000 ¹	27 fewer per 1000 (22 to 29)				
Superficial vein thrombosis	13 per 1000	7 fewer per 1000 (2 more to 11 fewer) Not statistically significant	RR 0.45 (0.18 to 1.13)	1804 (8)	⊕⊕⊕○ Moderate ³	
Oedema (range 0 to 10)	Mean 6 to 9 ²	Mean difference -4.7 (-4.5 to -4.9) Favours stockings		1246 (6)	⊕⊕○○ Low ⁴	Post-flight values measured on a scale from 0, no oedema, to 10, maximum oedema.
Symptomatic deep vein thrombosis	0 per 1000	---	---	2821 (9)		0 participants developed symptomatic DVT.
Pulmonary embolus	0 per 1000	---	---	2821 (9)		0 participants developed pulmonary embolus.
Death	0 per 1000	---	---	2821 (9)		0 participants died.
Adverse effects	---	---	---	1182 (4)		The tolerability of the stockings was described as very good with no complaints of side effects in 4 trials. ⁵

Control group risk

- for dichotomous outcomes: both relative and absolute effects
- SoF tables are build around a consistent relative effect
- up to three typical control group risk
- natural frequencies in the corresponding

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Without stockings	Corresponding risk With stockings				
Symptomatic deep vein thrombosis (DVT)	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed symptomatic DVT in these studies.
Symptom-less deep vein thrombosis	Low risk population ²		RR 0.10 (0.05 to 0.25)	2637 (9 studies)	⊕⊕⊕⊕ High	
	10 per 1000	1 per 1000 (0 to 3)				
	High risk population ²					
	30 per 1000	3 per 1000 (1 to 8)				

Assessing the quality of evidence

- authors will comment on quality of evidence
- high, moderate, low, very low
- GRADE system

Grades of Recommendation Assessment, Development and Evaluation

GRADE Working Group

Education and debate



Grading quality of evidence and strength of recommendations

GRADE Working Group

Clinical guidelines are only as good as the evidence and judgments they are based on. The GRADE approach aims to make it easier for users to assess the judgments behind recommendations

*Grade Working Group. CMAJ 2003, BMJ 2004, BMC 2004, BMC 2005

About GRADE

- Since 2000
- Researchers/guideline developers with interest in methodology
- Aim: to develop a **common, transparent and sensible** system for grading the quality of evidence and the strength of recommendations
- Evaluation of existing systems

GRADE Uptake

- Cochrane Collaboration
- World Health Organization
- American College of Chest Physicians
- UpToDate
- British Medical Journal
- American College of Physicians
- National Institute Clinical Excellence (NICE)
- American Thoracic Society
- European Society of Thoracic Surgeons
- Clinical Evidence
- Agency for Health Care Research and Quality (AHRQ)
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- Over 20 organizations

GRADE Quality of Evidence

Extent of confidence that estimate of effect is close to the quantity of interest

- high: considerable confidence in estimate of effect.
- moderate: further research likely to have impact on confidence in estimate, may change estimate.
- low: further research is very likely to impact on confidence, likely to change the estimate.
- very low: any estimate of effect is very uncertain

Determinants of quality

- RCTs start high
- observational studies start low
- what can lower quality?
 - detailed design and execution
 - inconsistency
 - indirectness
 - reporting bias
 - imprecision

What can raise quality?

- large magnitude can upgrade one level
 - very large two levels
 - common criteria
 - everyone used to do badly
 - almost everyone does well
 - Oral anticoagulation for mechanical heart valves
- dose response relation
(higher INR – increased bleeding)

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)

Settings: International air travel

Intervention: Compression stockings¹

Comparison: Without stockings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Without stockings	Corresponding risk With stockings				
Symptomatic deep vein thrombosis (DVT)	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed symptomatic DVT in these studies.
Symptom-less deep vein thrombosis	Low risk population ² 10 per 1000		RR 0.10 (0.05 to 0.25)	2637 (9 studies)	⊕⊕⊕⊕ High	
	High risk population ² 30 per 1000					
Superficial vein thrombosis	13 per 1000	6 per 1000 (2 to 15)	RR 0.45 (0.18 to 1.13)	1804 (8 studies)	⊕⊕⊕○ Moderate ³	
Oedema Post-flight values. Scale from 0, no oedema, to 10, maximum oedema.	The mean oedema ranged across control groups from 6 to 9.	The mean oedema in the intervention groups was on average 4.7 lower (4.5 to 4.9 lower).		1246 (6 studies)	⊕⊕○○ Low ⁴	
Pulmonary embolus	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed pulmonary embolus in these studies.
Death	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants died in these studies.
Adverse effects	See comment	See comment	Not estimable	1182 (4 studies)	See comment	The tolerability of the stockings was described as very good with no complaints of side effects in 4 studies. ⁵

*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: Relative Risk

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 All the stockings in the 9 trials included in this review were below-knee compression stockings. In four trials the compression strength was 20-30 mm Hg at the ankle. It was 10-20 mm Hg in the other four trials. Stockings come in different sizes. If a stocking is too tight around the knee it can prevent essential venous return causing the blood to pool around the knee. Compression stockings should be fitted properly. A stocking that is too tight could cut into the skin on a long flight and potentially cause ulceration and increased risk of DVT. Some stockings can be slightly thicker than normal leg covering and can be potentially restrictive with tight foot wear. It is a good idea to wear stockings around the house prior to travel to ensure a good, comfortable fitting. Stockings were put on 2 to 3 hours before the flight in most of the trials. The availability and cost of stockings can vary.

² Two trials recruited high risk participants defined as those with previous episodes of DVT, coagulation disorders, severe obesity, limited mobility due to bone or joint problems, neoplastic disease within the previous two years, large varicose veins or, in one of the studies, participants taller than 190 cm and heavier than 90 kg. The incidence for 7 trials that excluded high risk participants was 1.45% and the incidence for the 2 trials that recruited high-risk participants (with at least one risk factor) was 2.43%. We have rounded these off to 10 and 30 per 1,000 respectively.

³ The confidence interval crosses no difference and does not rule out a small increase.

⁴ The measurement of oedema was not validated or blinded to the intervention. All of these studies were conducted by the same investigators.

⁵ None of the other trials reported adverse effects, apart from 4 cases of superficial vein thrombosis in varicose veins in the knee region that were compressed by the upper edge of the stocking in one trial.

Comments

Compression stockings compared with no compression stockings for people taking long flights

Patients or population: Anyone taking a long flight (lasting more than 6 hours)

Settings: International air travel

Intervention: Compression stockings¹

Comparison: Without stockings

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Without stockings	Corresponding risk With stockings				
Symptomatic deep vein thrombosis (DVT)	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed symptomatic DVT in these studies.
Symptom-less deep vein thrombosis	Low risk population ²		RR 0.10 (0.05 to 0.25)	2637 (9 studies)	⊕⊕⊕⊕ High	
	10 per 1000	1 per 1000 (0 to 3)				
	High risk population ²					
	30 per 1000	3 per 1000 (1 to 8)				
Superficial vein thrombosis	13 per 1000	6 per 1000 (2 to 15)	RR 0.45 (0.18 to 1.13)	1804 (8 studies)	⊕⊕⊕○ Moderate ³	
Oedema Post-flight values. Scale from 0, no oedema, to 10, maximum oedema.	The mean oedema ranged across control groups from 6 to 9.	The mean oedema in the intervention groups was on average 4.7 lower (4.5 to 4.9 lower).		1246 (6 studies)	⊕⊕○○ Low ⁴	
Pulmonary embolus	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants developed pulmonary embolus in these studies.
Death	See comment	See comment	Not estimable	2821 (9 studies)	See comment	0 participants died in these studies.
Adverse effects	See comment	See comment	Not estimable	1182 (4 studies)	See comment	The tolerability of the stockings was described as very good with no complaints of side effects in 4 studies. ⁵

*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: Relative Risk

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.

How can we do all this?

- GRADE profiler software
- C sharp
- Windows based
- Help file
- Version 3.0 alpha
- Interaction with Revman
(import/export)

Drawing conclusions from reviews and SoF tables (1)

Implications for practice

- lay out benefits, harms and potential values
- “The decision for a patient with cancer to start heparin therapy for survival benefit should balance the benefits and downsides and integrate the patient’s values and preferences. Patients with a high preference for survival prolongation (even though that prolongation may be short) and limited aversion to bleeding who do not consider heparin therapy a burden may opt to use heparin, while those with aversion to bleeding and the burden of heparin therapy may not.”

Drawing conclusions from reviews and SoF tables (2)

Implications for resesarch

- EPICOT format
- consider the need for future research in the context of
 - evidence
 - ideal population of study
 - the manner in which the intervention should be administered
 - optimal comparator(s) of interest
 - the outcomes that trialists should measure
 - the time stamp of their recommendations

Summary

- summary of Findings (SoF) Tables present the main findings of a review in a simple table format
- separate element of the review
- phased-in over the next year
- additional non-modifiable table
- should help
 - reviewers drawing conclusions
 - authors interpreting results

Current and future work

- training and support to Cochrane review authors
- study to evaluate the effort required to prepare SoF Tables for each review
- SoF tables for diagnostic reviews