



Going from evidence to
recommendations

**Hvad kan GRADE bidrage med ved udarbejdelsen af
nationale kliniske retningslinjer?**

How can GRADE help with the development (and use) of clinical practice guidelines?

- What is evidence?
- What is GRADE?
- Confidence in recommendations
- A framework for going from evidence to a recommendation (or a decision)



What is evidence?

What is evidence?

“Evidence concerns facts (actual or asserted) intended for use in support of a conclusion”

- A fact is something known by experience or observation
- Evidence is used to support a conclusion; it is not the same as the conclusion

Examples

Facts

- I had prostate cancer detected by PSA screening and I am alive 10 years later.
- I operated on 100 patients with prostate cancer and none of them died from prostate cancer.
- My feeling is that the benefits of PSA screening are worth the harms and costs.

Conclusions

- PSA screening saved my life.
- Prostatectomy is effective.
- Well-informed patients would want to have PSA screening.

Is expert opinion evidence?

Expert opinion

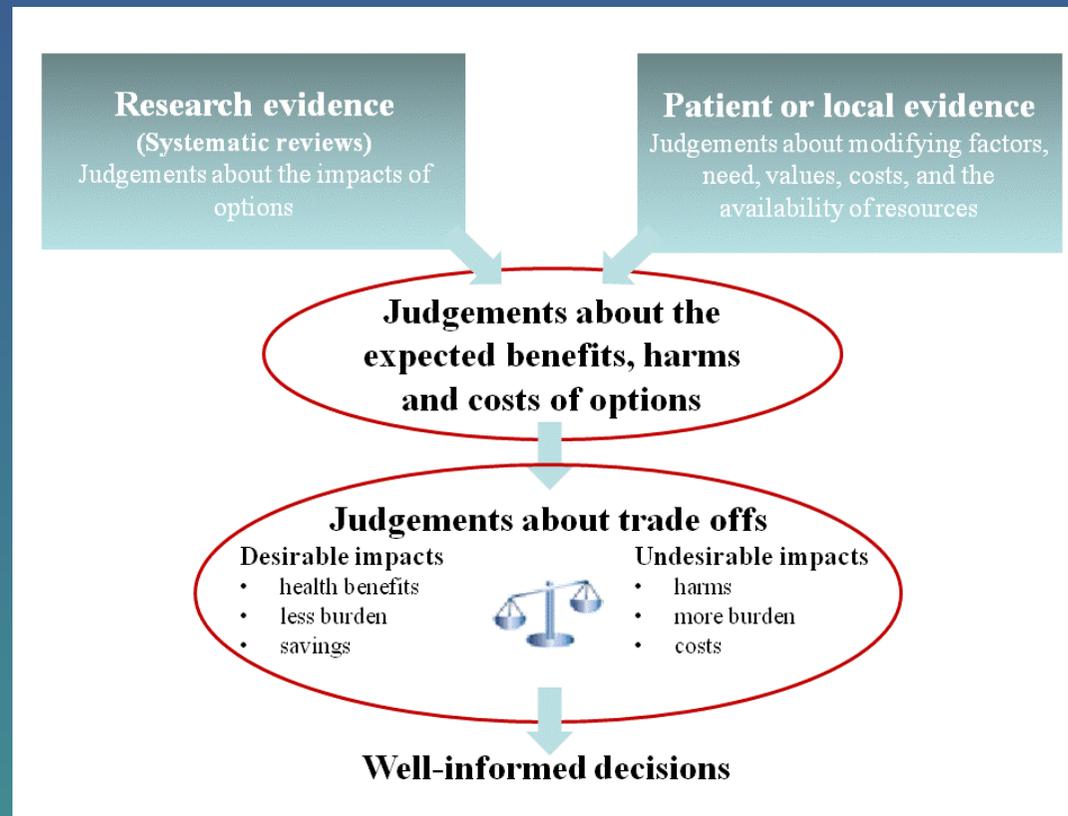
- Expert opinion is not the same as evidence
 - It combines facts, appraisal of those facts, and conclusions
 - There is evidence behind expert opinions
 - Expert opinion should be used appropriately by:
 - Identifying the facts (experience or observations) that are the basis of the opinions
 - Appraising the extent to which the facts support the conclusions (not how persuasive the expert is)

How should we decide how much confidence to place in evidence?

- Not all evidence is equally convincing
- How convincing evidence is (for effects) should be based on criteria such as:
 - What sort of observations (study design)
 - How well they were done (risk of bias)
 - How consistent they are (consistency)
 - How directly relevant they are (directness)
 - How many there are (precision)
 - How strong an association is (large effects)
- **NOT** on who says it or how they say it

What is the role of evidence in policy and practice?

- The role of evidence is to inform policy and practice
- Evidence is essential, but not sufficient
- Judgements are needed, including judgements about confidence in estimates of effect (the certainty of the evidence), what to expect in a specific setting, and trade-offs



Comments or questions about what
evidence is or its role in policy and
practice?

Why bother about grading the quality of evidence?

- People draw conclusions about
 - Confidence in estimates of effect
 - Confidence in recommendations
- Systematic and explicit approaches can help
 - protect against errors
 - resolve disagreements
 - facilitate critical appraisal
 - communicate information
- However, there has been wide variation in approaches

Many grading systems

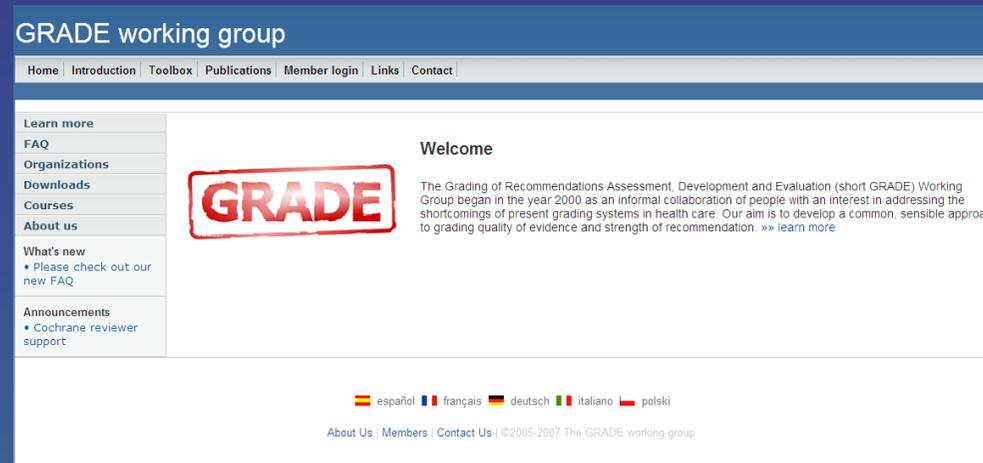
- US Preventative Services Task Force
- Scottish Intercollegiate Guidelines (SIGN)
- Australian NMRC
- Oxford Center for Evidence-based Medicine
- Professional organizations
 - AHA/ACC, ACCP, AAP, Endocrine society, etc....

Lots of confusion

Recommendation for use of oral anticoagulation in patients with atrial fibrillation and rheumatic mitral valve disease

Evidence	Recommendation	Organization
• B	Class I	➤ AHA
• C+	1	➤ ACCP
• IV	C	➤ SIGN

A common international grading system?



Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group ngggroup.org

- International group
 - ACCP, AHRQ, Australian NMRC, BMJ Clinical Evidence, CC, CDC, NICE, Oxford CEBM, SIGN, UpToDate, USPSTF, WHO
- > 200 contributors from 30 countries
 - methodologists, guideline developers, systematic reviewer authors, researchers, clinicians, editors
- ~ 40 meetings since 2001
 - ~50 participants
- Informal
 - Anyone can join the discussion list and become a member

mail@gradeworkinggroup.org

>70 organisations have endorsed or are using **GRADE**, including:

- American College of Physicians (ACC)
- Agency for Health Care Research and Quality (AHRQ)
- American College of Chest Physicians (ACCP)
- BMJ Clinical Evidence
- British Medical Journal
- Canadian Task Force on Preventive Health Care
- Cochrane Collaboration
- EBM Guidelines
- Kaiser Permanente
- National Institute for Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- UpToDate
- World Health Organization



www.gradeworkinggroup.org

Organizations that have endorsed or that are using GRADE*

Some organizations in their enthusiasm to use GRADE, have modified the GRADE approach. We recommend against such modifications because the elements of the GRADE process are interlinked, because modifications may confuse some evidence and guideline users, and because such changes compromise the goal of a single system with which clinicians, policy-makers and patients can become familiar.

	World Health Organization	World Health Organization - International	<i>Example</i>
		Endocrine Society - USA	<i>Example</i>
		American College of Chest Physicians - USA	<i>Example</i>
		UpToDate - Putting Clinical Information Into Practice - USA	<i>UTD GRADE tutorial</i>
		Agenzia sanitaria regionale, Bologna - Italia	
		Health Quality Ontario, Ontario - Canada	<i>Example</i>
		Surviving Sepsis - International	
		Ärztliches Zentrum für Qualität in der Medizin - Germany	
		American Thoracic Society - USA	<i>Example</i>
		American College of Physicians - USA	<i>Example</i>
		The Cochrane Collaboration - International	

2008;336;924-926 *BMJ*
2008;336;995-998 *BMJ*
2008;336;1049-1051 *BMJ*

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evidence and the strength of recommendations. This article explores the advantages of the GRADE system, which is increasingly being adopted by organisations worldwide

Guideline developers around the world are inconsistent in how they rate quality of evidence and grade strength of recommendations. As a result, guideline users face challenges in understanding the messages that grading systems try to communicate. Since 2006 the *BMJ* has requested in its “Instructions to Authors” on *bmj.com* that authors should preferably use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading evidence when submitting a clinical guidelines article.

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advantages and disadvantages but also by their confidence in these estimates. The cartoon depicting the weather forecaster’s uncertainty captures the difference between an assessment of the likelihood of an outcome and the confidence in that assessment (figure). The usefulness of an estimate of the magnitude of intervention effects depends on our confidence in that estimate.

Expert clinicians and organisations offering recommendations to the clinical community have often erred as a result of not taking sufficient account of the quality

www.gradeworkinggroup.org

Questions or comments about
the GRADE Working Group?

Confidence in recommendations

“Strength of recommendation”

GRADE

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects.

Desirable effects

- health benefits
- less burden
- savings



Undesirable effects

- harms
- more burden
- costs

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: going from evidence to recommendations

BMJ 2008;336;1049-1051

Categories of recommendations

GRADE

Although the degree of confidence is a continuum, we suggest using two categories: strong and weak.

- **Strong recommendation:** the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
- **Weak recommendation:** the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident.

Recommend



Suggest



Implications of strong and weak recommendations for patients

- Strong - Most people in your situation would want the recommended course of action and only a small proportion would not
- Weak - The majority of people in your situation would want the recommended course of action, but many would not

Implications of strong and weak recommendations for clinicians

- Strong - Most patients should receive the recommended course of action
- Weak - Be prepared to help patients to make a decision that is consistent with their own values

Determinants of strength of recommendation

GRADE

Factors	Impact on the strength of a recommendation
Balance between desirable and undesirable effects	Larger the difference between the desirable and undesirable effects, more likely a strong recommendation warranted. Narrower the gradient, more likely weak recommendation warranted
Certainty (quality) of the evidence	Higher the quality of evidence, more likely a strong recommendation warranted
Relative importance of the outcomes (“values and preferences”)	More variability in values and preferences, or more uncertainty in values and preferences, more likely weak recommendation warranted
Costs (resource use)	Higher the costs of an intervention – that is, the more resources consumed – less likely a strong recommendation warranted

An example

Should patients with atrial fibrillation be treated with dabigatran or warfarin to reduce the risk of ischemic stroke?

The NEW ENGLAND
JOURNAL *of* MEDICINE

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

N Engl J Med 2009;361.

RE-LY

- 18,133 patients
 - warfarin, dabigatran 110 and 150
 - median follow-up 2 years
- International normalized ratio (INR)
“adjusted locally”
 - regular INRs fed back to participating centers with advice for optimal control
- Dabigatran no monitoring
 - no antidote
- Focus: 150 mg. dose

Summary of Findings: Dabigatran (150 mg) vs warfarin for atrial fibrillation

Outcome Follow-up: 2 yrs	Risk ratio (95% CI)	Estimated absolute effects 1 year time frame			Certainty of the effect
		Warfarin (per 1000)*	Dabigatran (per 1000)	Difference (per 1000)	
Death	0.89 (0.79 to 1.01)	38	34	4 fewer (8 to 0 fewer)	⊕⊕⊕○ Moderate
Nonfatal stroke (CHADS ₂ 2)	0.64 (0.51 to 0.81)	17	11	6 fewer (2 to 8 fewer)	⊕⊕⊕⊕ High
Nonfatal major extracranial bleeding	1.07 (0.83 to 1.08)	70	66	1 more (1 fewer to 3 more)	⊕⊕⊕○ Moderate
Myocardial infarction	1.38 (1.00 to 1.91)	5	7	2 more (0 to 5 more)	⊕⊕⊕○ Moderate
Burden of treatment	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits		Dabigatran: once daily medication		Less ⊕⊕⊕⊕ High

Other potential undesirable effects

The risk of rare severe adverse effects from dabigatran is uncertain.

Compliance might potentially be more of a problem with dabigatran than warfarin since monitoring and frequent clinic visits are not needed, but there is not evidence to support or refute this.

There is currently no antidote to dabigatran. This is a concern for healthcare providers who have to manage bleeding patients receiving dabigatran and might lead to worse outcomes in such patients.

* Baseline risks taken from ACCP Antithrombotic Guidelines 9th ed (Chest. 2012;141(2_suppl):e531S-e575S)

Dabigatran (150 mg) vs warfarin for atrial fibrillation

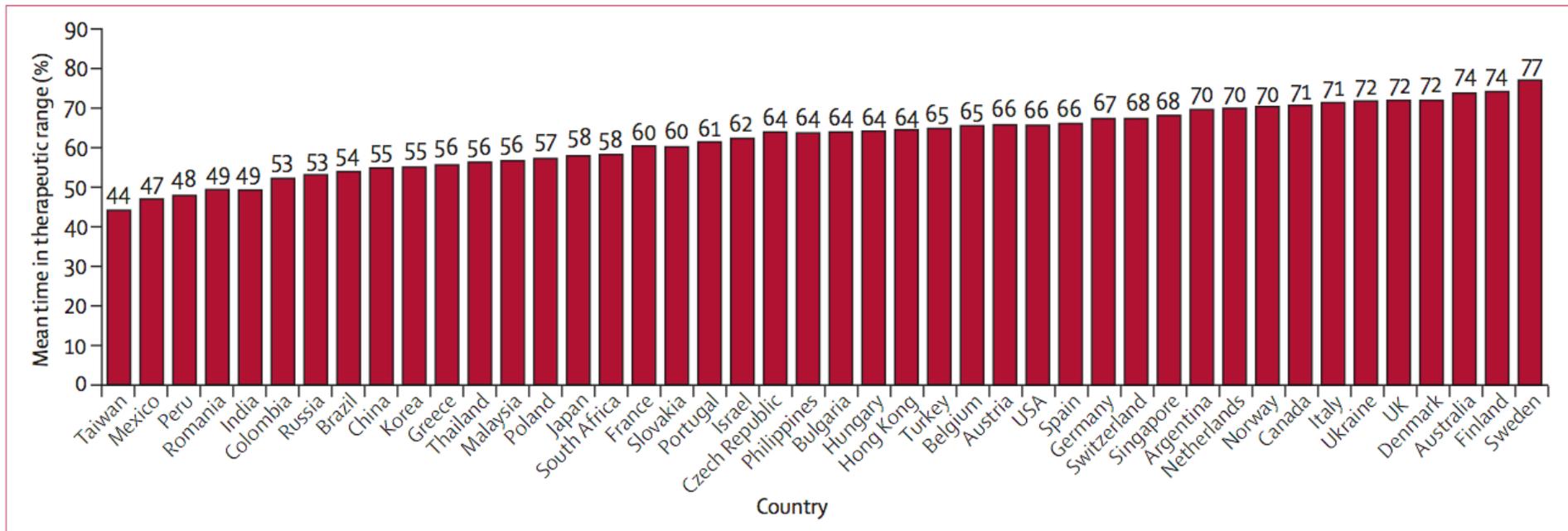
Factors that can weaken the strength of a recommendation	Judgment	Explanation
Small net benefit	<input type="checkbox"/> Yes <input type="checkbox"/> No	How important is 6 fewer nonfatal strokes, 4 fewer deaths and less burden of treatment compared to 2 more myocardial infarctions and uncertainty about serious adverse effects per 1000 patients over 1 year?
Low certainty of evidence	<input type="checkbox"/> Yes <input type="checkbox"/> No	The certainty of the evidence is high for nonfatal strokes and moderate for other outcomes.
Uncertainty or differences in how much patients value the outcomes of interest	<input type="checkbox"/> Yes <input type="checkbox"/> No	The estimated incremental lifetime gain in quality adjusted life is 3 to 4 months.
High costs	<input type="checkbox"/> Yes <input type="checkbox"/> No	The cost of dabigatran is about 68 000 kr more per year (paid for by the government).

Should patients with atrial fibrillation be treated with dabigatran or warfarin to reduce the risk of ischemic stroke?

	Strong	Weak		Weak	Strong
Your view of the balance of desirable and undesirable consequences of the intervention	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	Consequences equally balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
Recommendation	We recommend warfarin	We suggest warfarin	No specific recommendation	We suggest dabigatran	We recommend dabigatran
Vote					

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY investigators



Sub-group: warfarin control

- Calculated mean time in the therapeutic range (TTR) in each centre
 - included 906/951 sites
- Quartiles:
 - < 57.1%
 - 57.1–65.5%
 - 65.5–72.6%
 - > 72.6%

Results by quartile

Mean TTR per centre

	poorest < 57.1%	better 57.1 - 65.5	better yet 65.5 - 72.6	best > 72.6%	p-value interaction
Death	0.67 (0.53-0.85)	0.92 (0.71-1.18)	0.98 (0.75-1.28)	1.08 (0.81-1.44)	0.052
Stroke/embolism	0.57 (0.37-0.88)	0.50 (0.33-0.77)	0.69 (0.44-1.09)	0.95 (0.61-1.48)	0.20
Major bleeding	0.71 (0.52-0.96)	0.81 (0.62-1.05)	1.13 (0.87-1.48)	1.16 (0.88-1.54)	0.03

Criteria to assess the credibility of subgroup analyses

Design

- Is the subgroup variable a characteristic measured at baseline or after randomisation?
- **Is the effect suggested by comparisons within rather than between studies?**
- **Was the hypothesis specified a priori?**
- **Was the direction of the subgroup effect specified a priori?**
- **Was the subgroup effect one of a small number of hypothesised effects tested?**

Analysis

- **Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?**
- Is the significant subgroup effect independent?

Context

- **Is the size of the subgroup effect large?**
- **Is the interaction consistent across studies?**
- Is the interaction consistent across closely related outcomes within the study?
- Is there indirect evidence that supports the hypothesised interaction (biological rationale)?

Credibility of subgroup analyses for mean TTR per centre for Dabigatran vs warfarin

- Is effect suggested by comparisons within studies? *yes*
- Was hypothesis specified a priori? *yes*
- Was direction of effect specified a priori? *yes*
- Small number of hypothesised effects tested? *no*
- Likelihood that chance explains effect? *$p = 0.052, 0.20, 0.03$*
- Consistent across closely related outcomes? *yes*
- Dose-response *yes*
- Indirect evidence (biological rationale)? *yes*

Credibility of the sub-group analysis

Very low	Low	Moderate	High
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Dabigatran (150 mg) vs warfarin for atrial fibrillation with good INR control (TTR > 72.6%)

Factors that can weaken the strength of a recommendation	Judgment	Explanation
Small net benefit	<input type="checkbox"/> Yes <input type="checkbox"/> No	How important is less burden of treatment compared to 4 more heart attacks and uncertainty about serious adverse effects per 1000 patients (over 1 year)?
Low certainty of evidence	<input type="checkbox"/> Yes <input type="checkbox"/> No	The certainty of the evidence is moderate.
Uncertainty or differences in how much patients value the outcomes of interest	<input type="checkbox"/> Yes <input type="checkbox"/> No	
High costs	<input type="checkbox"/> Yes <input type="checkbox"/> No	The cost of dabigatran is about 68 000 kr more per year (paid for by the government).

Should patients with atrial fibrillation be treated with dabigatran or warfarin to reduce the risk of ischemic stroke?

	Strong	Weak		Weak	Strong
Your view of the balance of desirable and undesirable consequences of the intervention	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	Consequences equally balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
Recommendation	We recommend not to screen	We suggest not to screen	No specific recommendation	We suggest to screen	We recommend to screen
Vote					

Questions or comments?

Experience with using the
GRADE framework for
judgements about the strength
of recommendations?

A personal decision

For example:

Should you, a relative or a close friend with atrial fibrillation take dabigatran or warfarin to reduce the risk of ischemic stroke?

Should you, a relative or a close friend with atrial fibrillation take dabigatran or warfarin?

Factors that can weaken the strength of a recommendation	Judgement	Explanation
Small net benefit	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Low certainty of evidence	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Uncertainty or differences in “values and preferences”	<input type="checkbox"/> Yes <input type="checkbox"/> No	Variability in values is not relevant. How certain are you about your values (or those of your relative or close friend)?
High costs	<input type="checkbox"/> Yes <input type="checkbox"/> No	Only your (or her or his) out of pocket costs are relevant.

Should you, a relative or a close friend with atrial fibrillation take dabigatran or warfarin to reduce the risk of ischemic stroke?

	Yes	Probably	Don't know	Probably not	No
Your view of the balance of desirable and undesirable consequences of the intervention	Desirable consequences clearly outweigh undesirable consequences	Desirable consequences probably outweigh undesirable consequences	Consequences equally balanced or uncertain	Undesirable consequences probably outweigh desirable consequences	Undesirable consequences clearly outweigh desirable consequences
Decision	Yes	Consider using a decisions aid		No	

Questions or comments about
personal decisions?

Recommendations from a health system or
population perspective

Should clinicians working in the public health service recommend dabigatran or warfarin (from a population perspective)?

Factors that can weaken the strength of a recommendation	Judgement	Explanation
Small net benefit	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Low certainty of evidence	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Uncertainty or differences in “values and preferences”	<input type="checkbox"/> Yes <input type="checkbox"/> No	
High costs	<input type="checkbox"/> Yes <input type="checkbox"/> No	Costs (and savings) to the government, insurer or public health service are relevant.

Should the government establish antithrombotic teams that are responsible for antithrombotic therapy?

	No	Probably not	Don't know	Probably	Yes
Your view of the balance of desirable and undesirable consequences of the intervention (including costs)	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	Consequences equally balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
Recommendation	We recommend against a screening mammography programme	We recommend the option <ul style="list-style-type: none"> □ Only in the context of rigorous research □ Only with monitoring and evaluation □ Only in specific contexts 			We recommend a screening mammography programme
Vote					

Should the government pay for dabigatran?

Factors that can weaken the strength of a recommendation	Judgement	Explanation
Small net benefit	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Low certainty of evidence	<input type="checkbox"/> Yes <input type="checkbox"/> No	
Uncertainty or differences in “values and preferences”	<input type="checkbox"/> Yes <input type="checkbox"/> No	Variability in “values and preferences” is not relevant
High costs	<input type="checkbox"/> Yes <input type="checkbox"/> No	Costs (and savings) to the government, insurer or public health service are relevant.

Should the government pay for dabigatran?

	No	Probably not	Don't know	Probably	Yes
Your view of the balance of desirable and undesirable consequences of the intervention (including costs)	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	Consequences equally balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
Recommendation	We recommend against coverage	We recommend <ul style="list-style-type: none"> <input type="checkbox"/> Coverage with evidence development <input type="checkbox"/> Restricted coverage <input type="checkbox"/> Coverage with price reduction 			We recommend coverage
Vote					

DECIDE framework for going from evidence to recommendations (or decisions)

- Clinical practice guidelines
 - Individual patient perspective
 - Health system perspective
- Health system and public health decisions
- Coverage
- Diagnostic tests

DECIDE



GRADE



The **DECIDE** project has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under Grant Agreement no 258583

Purpose

To help guideline panels (and decision makers) move from evidence to a recommendation or decision by

- Informing judgements about the pros and cons of each option (intervention) that is considered
- Ensuring that important factors that determine a decision (criteria) are considered
- Providing a concise summary of the best available research evidence to inform judgements about each criterion
- Helping to structure discussion and identify reasons for disagreements
- Making the basis for a decision transparent to those affected
- Helping decision makers go from a recommendation to a decision

Development of the frameworks

- Part of the DECIDE project
- An iterative process informed by
 - GRADE approach to clinical practice guidelines
 - Review of relevant literature
 - Brain storming
 - Feedback from stakeholders
 - Application of the framework to examples
 - Surveys of (e.g. of policymakers)
 - User testing
 - Trials



- **Criteria** on which a recommendation is based
- **Judgements** that must be made in relation to each criterion
- **Research evidence** to inform each judgement
- **Additional considerations** that inform or explain each judgement

Conclusions

- The ***overall judgement across all*** criteria of whether the desirable consequences of the option being considered outweigh the undesirable consequences
- The ***type of recommendation***
- The ***recommendation text*** in plain language
- The ***justification*** for the recommendation, flowing from the judgements in relation to the criteria
- ***Subgroup considerations***
- ***Implementation considerations***
- ***Monitoring and evaluation considerations***
- ***Research priorities***

An illustration of a recommendation from a government perspective:

Should clinicians working in the public health service recommend dabigatran or warfarin for atrial fibrillation?



Prepared by: Vijay Shukla, Karen Lee, Andy Oxman
Date: 22 January 2012 (revised 26 October 2013)

Evidence to recommendation framework – Clinical practice guideline (government perspective)

Should clinicians working in the public health service recommend dabigatran or warfarin to patients with atrial fibrillation?

Problem: Atrial fibrillation (high risk of stroke)

Intervention: Dabigatran

Comparison: Warfarin

Setting: Denmark

Perspective: Government

Background: Warfarin reduces the risk for ischemic stroke in patients with atrial fibrillation, but increases the risk for hemorrhage and requires frequent blood tests and clinic visits to monitor the international normalized ratio (INR) and adjust the dose. Apixaban, dabigatran and rivaroxaban are newer fixed-dose, oral anti-coagulants, each of which has been compared to warfarin in randomized trials.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	Is the problem a priority?	No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <input type="checkbox"/> Varies <input type="checkbox"/>	The risk of complications varies depending on how well INR is controlled with warfarin. Average risks were 8.1% for death, 3.4% for nonfatal stroke, and 7% for nonfatal major extracranial bleeds over 2 years in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial.	

The more serious or urgent a problem is, the more likely it is that an option that addresses the problem will be a priority.

Should clinicians working in the public health service recommend dabigatran or warfarin for atrial fibrillation?

GRADE
DECIDE

Problem: Atrial fibrillation

Intervention: Dabigatran

Comparison: Warfarin

Setting: Denmark

Perspective: Government

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																						
<p>VALUES</p> <p>Is there important uncertainty about how much people value the main outcomes?</p>	<table border="1"> <thead> <tr> <th>Important uncertainty or variability</th> <th>Possibly important uncertainty or variability</th> <th>Probably no important uncertainty or variability</th> <th>No important uncertainty or variability</th> <th>No known undesirable outcomes</th> </tr> </thead> <tbody> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </tbody> </table> <p>Detailed judgements</p>	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes	<input type="checkbox"/>	<p>Quality adjusted life expectancy</p> <table border="1"> <thead> <tr> <th></th> <th>Warfarin</th> <th>Dabigatran</th> <th>Difference</th> </tr> </thead> <tbody> <tr> <td>QALYs</td> <td>8.203</td> <td>8.495</td> <td>0.292</td> </tr> </tbody> </table> <p>Relative importance of the outcomes</p> <table border="1"> <thead> <tr> <th>Outcome</th> <th>Utility values (range considered)</th> </tr> </thead> <tbody> <tr> <td>Death</td> <td>0</td> </tr> <tr> <td>Previous stroke Rankin score 5</td> <td>0.11 (0.22, 0.52)</td> </tr> <tr> <td>Rankin score 3-4</td> <td>0.39 (0.22, 0.52)</td> </tr> <tr> <td>Minor stroke</td> <td>0.75 (0.55, 0.80)</td> </tr> </tbody> </table> <p>Decrements associated with events*</p> <table border="1"> <tbody> <tr> <td>MI</td> <td>0.125</td> </tr> <tr> <td>ICH</td> <td>0.181</td> </tr> <tr> <td>Major bleed</td> <td>0.092 (0.092, 0.184)</td> </tr> <tr> <td>PE</td> <td>0.022</td> </tr> <tr> <td>Minor bleed</td> <td>0.013 (0.013, 0.026)</td> </tr> </tbody> </table> <p>*Utility decrements calibrated and applied for 1 month</p>		Warfarin	Dabigatran	Difference	QALYs	8.203	8.495	0.292	Outcome	Utility values (range considered)	Death	0	Previous stroke Rankin score 5	0.11 (0.22, 0.52)	Rankin score 3-4	0.39 (0.22, 0.52)	Minor stroke	0.75 (0.55, 0.80)	MI	0.125	ICH	0.181	Major bleed	0.092 (0.092, 0.184)	PE	0.022	Minor bleed	0.013 (0.013, 0.026)	<p>The utility values are consistent with other values identified in a systematic review.</p> <p>The impact of stroke outcomes persists over a longer period of time (in terms of disability) while other events are associated with impacts to quality of life that affect a finite period of time. It is assumed that there are minimal long term implications associated with bleeding events.</p>				
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The more likely it is that different (plausible) values would lead to different decisions, the less certain it is that an option should be recommended (or the more important it is to obtain evidence of the values of those affected by the option).

Should clinicians working in the public health service recommend dabigatran or warfarin for atrial fibrillation?



Problem: Atrial fibrillation

Intervention: Dabigatran

Comparison: Warfarin

Setting: Denmark

Perspective: Government

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																																		
BENEFITS & HARMS OF THE OPTIONS	What is the overall certainty of the evidence of effectiveness?	<p>No included studies <input type="checkbox"/></p> <p>Very low <input type="checkbox"/> Low <input type="checkbox"/> Moderate <input type="checkbox"/> High <input type="checkbox"/></p>	<p>Summary of findings: Dabigatran (150 mg) vs warfarin for atrial fibrillation</p> <table border="1"> <thead> <tr> <th rowspan="2">Outcome</th> <th rowspan="2">Risk ratio (95% CI)</th> <th colspan="3">Estimated absolute effects</th> <th rowspan="2">Certainty of the effect</th> </tr> <tr> <th colspan="3">1 year time frame</th> </tr> <tr> <th>Warfarin (per 1000)*</th> <th>Dabigatran (per 1000)</th> <th>Difference (per 1000)</th> <th colspan="2"></th> </tr> </thead> <tbody> <tr> <td colspan="6"><i>Follow-up: 2 yrs</i></td> </tr> <tr> <td>Death</td> <td>0.89 (0.79 to 1.01)</td> <td>38</td> <td>34</td> <td>4 fewer (8 to 0 fewer)</td> <td>⊕⊕⊕○ Moderate</td> </tr> <tr> <td>Nonfatal stroke (CHADS₂ 2)</td> <td>0.64 (0.51 to 0.81)</td> <td>17</td> <td>11</td> <td>6 fewer (2 to 8 fewer)</td> <td>⊕⊕⊕⊕ High</td> </tr> <tr> <td>Nonfatal major extracranial bleeding</td> <td>1.07 (0.83 to 1.08)</td> <td>70</td> <td>66</td> <td>1 more (1 fewer to 3 more)</td> <td>⊕⊕⊕○ Moderate</td> </tr> <tr> <td>Myocardial infarction</td> <td>1.38 (1.00 to 1.91)</td> <td>5</td> <td>7</td> <td>2 more (0 to 5 more)</td> <td>⊕⊕⊕○ Moderate</td> </tr> <tr> <td>Burden of treatment</td> <td>Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits</td> <td>Dabigatran: once daily medication</td> <td colspan="2">Less</td> <td>⊕⊕⊕⊕ High</td> </tr> </tbody> </table> <p><i>Other potential undesirable effects</i></p> <p>The risk of rare severe adverse effects from dabigatran is uncertain.</p> <p>Compliance might potentially be more of a problem with dabigatran than warfarin since monitoring and frequent clinic visits are not needed, but there is not evidence to support or refute this.</p> <p>There is currently no antidote to dabigatran. This is a concern for healthcare providers who have to manage bleeding patients receiving dabigatran and might lead to worse outcomes in such patients.</p> <p>*Baseline risks taken from ACCP Antithrombotic Guidelines 9th ed (Chest. 2012;141(2_suppl):e531S-e575S)</p> <p>Link to detailed evidence profile</p> <p>Subgroup considerations: Link(s) to summary of findings and judgments for subgroups</p>	Outcome	Risk ratio (95% CI)	Estimated absolute effects			Certainty of the effect	1 year time frame			Warfarin (per 1000)*	Dabigatran (per 1000)	Difference (per 1000)			<i>Follow-up: 2 yrs</i>						Death	0.89 (0.79 to 1.01)	38	34	4 fewer (8 to 0 fewer)	⊕⊕⊕○ Moderate	Nonfatal stroke (CHADS ₂ 2)	0.64 (0.51 to 0.81)	17	11	6 fewer (2 to 8 fewer)	⊕⊕⊕⊕ High	Nonfatal major extracranial bleeding	1.07 (0.83 to 1.08)	70	66	1 more (1 fewer to 3 more)	⊕⊕⊕○ Moderate	Myocardial infarction	1.38 (1.00 to 1.91)	5	7	2 more (0 to 5 more)	⊕⊕⊕○ Moderate	Burden of treatment	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits	Dabigatran: once daily medication	Less		⊕⊕⊕⊕ High	<p>Subgroup considerations: Different TTR (TTR < 66%, TTR ≥ 66%) (e.g. consider a separate recommendation for patients with poor INR control with warfarin despite documented adequate medication compliance)</p>
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Do the desirable effects outweigh the undesirable effects?	<p>No <input type="checkbox"/> Probably No <input type="checkbox"/> Uncertain <input type="checkbox"/> Probably Yes <input type="checkbox"/> Yes <input type="checkbox"/> Varies <input type="checkbox"/></p> <p>Detailed judgements</p>																																																					

Should clinicians working in the public health service recommend dabigatran or warfarin for atrial fibrillation?



Problem: Atrial fibrillation

Intervention: Dabigatran

Comparison: Warfarin

Setting: Denmark

Perspective: Government

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																								
RESOURCE USE	How large are the resource requirements?	<table border="0"> <tr> <td>Large costs</td> <td>Moderate costs</td> <td>Small</td> <td>Moderate savings</td> <td>Large savings</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Large costs	Moderate costs	Small	Moderate savings	Large savings	Varies	<input type="checkbox"/>	<p>Total cost for 100,000 patients (kroner)</p> <table border="1"> <thead> <tr> <th></th> <th>Warfarin</th> <th>Dabigatran</th> <th>Difference</th> </tr> </thead> <tbody> <tr> <td>Yearly medication</td> <td>148 million</td> <td>6,91 billion</td> <td>+ 6.77 billion</td> </tr> <tr> <td>Total lifetime cost</td> <td>1.57 billion</td> <td>75.1 billion</td> <td>+73.5 billion</td> </tr> </tbody> </table>		Warfarin	Dabigatran	Difference	Yearly medication	148 million	6,91 billion	+ 6.77 billion	Total lifetime cost	1.57 billion	75.1 billion	+73.5 billion						
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How large is the incremental cost relative to the net benefit?	<table border="0"> <tr> <td>Very large ICER</td> <td>Large ICER</td> <td>Moderate ICER</td> <td>Small ICER</td> <td>Savings</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p style="text-align: center;">Detailed judgements</p>	Very large ICER	Large ICER	Moderate ICER	Small ICER	Savings	Varies	<input type="checkbox"/>	<table border="1"> <thead> <tr> <th>Incremental cost</th> <th>Incremental effect</th> <th>ICER</th> <th>Uncertainty†</th> </tr> </thead> <tbody> <tr> <td>78,414 kr</td> <td>0.292 QALY</td> <td>268,539 kr per QALY</td> <td>The ICER was less than 300,000 kr in 55.6% of simulations.‡</td> </tr> </tbody> </table> <p>† Monte Carlo simulations varying all variables simultaneously ‡ Results were relatively insensitive to one-way sensitivity analyses: - For lower prices of dabigatran, the cost effectiveness of dabigatran improved. - For shorter time horizons, dabigatran was less cost-effective 10 year time horizon, only cost effective if willing to pay > 350,000 kr/QALY 2 year time horizon only cost effective if willing to pay > 2.2 million kr/QALY</p> <p>Subgroup considerations: Link(s) to findings and judgments for subgroups</p>	Incremental cost	Incremental effect	ICER	Uncertainty†	78,414 kr	0.292 QALY	268,539 kr per QALY	The ICER was less than 300,000 kr in 55.6% of simulations.‡	<p>Subgroup considerations: TTR (TTR < 66%, TTR ≥ 66%) Age (55-64, 65-74, 75-84) Risk of stroke (</p>										
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The less acceptable an option is to key stakeholders, the less likely it is that it should be recommended, or if it is recommended, the more likely it is that the recommendation should include an implementation strategy to address concerns about acceptability. Unacceptability may be due to some stakeholders:

- Not accepting the distribution of the benefits, harms and costs
- Not accepting costs or undesirable effects in the short term for desirable effects (benefits) in the future
- Attaching more value to the undesirable consequences than to the desirable consequences
- Morally disapproving (i.e. in relationship to ethical principles such as autonomy)



Problem: Atrial fibrillation

Intervention: Dabigatran

Comparison: Warfarin

Setting: Denmark

Perspective: Government

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS												
EQUITY	What would be the impact on health inequities?	<table border="0"> <tr> <td>Increased</td> <td>Probably increased</td> <td>Uncertain</td> <td>Probably reduced</td> <td>Reduced</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	Increased	Probably increased	Uncertain	Probably reduced	Reduced	Varies	<input type="checkbox"/>		Dabigatran might reduce inequities for people whose INR is poorly controlled or who do not have easy access to testing.					
Increased	Probably increased	Uncertain	Probably reduced	Reduced	Varies											
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>											
ACCEPTABILITY	Is the option acceptable to key stakeholders?	<table border="0"> <tr> <td>No</td> <td>Probably No</td> <td>Uncertain</td> <td>Probably Yes</td> <td>Yes</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	No	Probably No	Uncertain	Probably Yes	Yes	Varies	<input type="checkbox"/>							
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FEASIBILITY	Is the option feasible to implement?	<table border="0"> <tr> <td>No</td> <td>Probably No</td> <td>Uncertain</td> <td>Probably Yes</td> <td>Yes</td> <td>Varies</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table>	No	Probably No	Uncertain	Probably Yes	Yes	Varies	<input type="checkbox"/>		It might be difficult to restrict the use of dabigatran to people who would benefit sufficiently to warrant the cost.					
No	Probably No	Uncertain	Probably Yes	Yes	Varies											
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>											

The more barriers there are to implementing the option that would be difficult to overcome, the less likely it is that it should be recommended.

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Overall judgement across all criteria

Undesirable consequences *clearly outweigh* desirable consequences in most settings

Undesirable consequences *probably outweigh* desirable consequences in most settings

The balance between desirable and undesirable consequences *is closely balanced or uncertain*

Desirable consequences *probably outweigh* undesirable consequences in most settings

Desirable consequences *clearly outweigh* undesirable consequences in most settings

Type of recommendation

We recommend not offering the intervention

We suggest not offering the intervention

We suggest offering the intervention

We recommend offering the intervention

Recommendation (text)

[Recommendation]

Justification

[Justification]

Subgroup considerations

[Subgroup considerations]

Implementation considerations

[Implementation considerations]

Monitoring and evaluation considerations

[Monitoring and evaluation]

Research priorities

[Research priorities]

An interactive Evidence to Recommendation Framework

Guideline developers (e.g. NKR) can

- Create templates for developing guidelines
- Standardize terminology, explanations and guidance
- Generate user-friendly, layered guidelines



Everything should be
made as simple as
possible, but not simpler.

Albert Einstein

Tak!