Mapping from SORT to GRADE

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Disclosures

- Brian S. Alper MD, MSPH, FAAFP is editor-in-chief for DynaMed (published by EBSCO) and medical director for EBSCO Information Services (full-time employee)

- Allen Shaughnessy, PharmD, MMedEd is a Professor of Family Medicine at Tufts University. He is a co-investigator and received contract support from EBSCO for this work.

Background - Grading quality of evidence and strength of recommendations

Problem: > 100 different systems

- Substantial confusion in interpreting trustworthiness of evidence, degree of obligation for recommendations, and how these two concepts are related
- Concepts from one guideline do not easily translate to seemingly similar labels in another guideline

Solution

- Collaborative effort across reference sources and guideline developers to produce a unifying system
- Continued effort to maintain, improve, and educate in use of the system
- Strength of Recommendation Taxonomy (SORT)
- Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)

SORT

- Started in 2004
- Initially created by 5 family medicine and primary care journals + 1 network (FPIN)
- Quality of Evidence:
  - Level 1 (good-quality patient-oriented evidence)
  - Level 2 (limited-quality patient-oriented evidence)
  - Level 3 (other evidence)
- QoE Assessment
  - Level 2 if risk of bias, inconsistency, or inadequate statistical power

GRADE

- Started in 2000
- Used by > 70 guideline developers and by Cochrane
- Quality of Evidence:
  - High (A)
  - Moderate (B)
  - Low (C)
  - Very Low (D)
- QoE Assessment
  - Downgrade for risk of bias, indirectness, inconsistency, imprecision, publication bias
  - Upgrade for large effect size+

SORT

- Strength of Recommendation
  - A (consistent level 1 evidence)
  - B (inconsistent, single level 1, or level 2 evidence)
  - C (no patient-oriented evidence)
- SoR Determination:
  - Level of evidence
- Further Development
  - Limited to DynaMed use and extension of level of evidence criteria

GRADE

- Strength of Recommendation
  - Strong (1)
  - Weak (2)
- SoR Determination:
  - Benefits vs. harms
  - Values and preferences
  - Resource use
- Further Development
  - > 300 guideline developers and contributors have provided continued feedback and adjustment

Background - DynaMed and SORT

- DynaMed adopted SORT in 2004
  - Added words to the labels
    - Level 1 (likely reliable) evidence
    - Level 2 (mid-level) evidence
    - Level 3 (lacking direct) evidence
  - Added more detailed, explicit criteria for Level 1 evidence (elevating “good-quality” to “high-quality”)
- DynaMed dropped A/B/C strength of recommendation part of SORT in 2011 as this was poorly developed for classifying issues based on factors other than evidence quality
- **DynaMed now has > 56,000 level of evidence labels**

DynaMed: Anticoagulant therapy for venous thromboembolism - Windows Internet Explorer
http://web.ebscohost.com/dynamed/detail?vid=38&sid=e4c1fde0-db48-40fc-a3a8-cea33a8b000a%40sessionmgr158&hid=26&bdata=JnNpdGU9ZHluYW1lZC1saXZlJnNjb3BlPXNpdGU%3d#db=dme&AN=115193&anchor=anc-552
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Anticoagulant therapy for venous thromboembolism

Efficacy of apixaban:

- **apixaban is at least as effective for treatment of acute venous thromboembolism as conventional therapy and reduces bleeding risk (level 1 [likely reliable] evidence)**
  - based on randomized noninferiority trial
  - 5,395 adults (mean age 57 years) with acute symptomatic proximal deep vein thrombosis or pulmonary embolism were randomized to 1 of 2 interventions and followed for 7 months
    - conventional therapy with enoxaparin 1 mg/kg subcutaneously every 12 hours for ≥ 5 days plus warfarin with target international normalized ratio (INR) 2-3 for 6 months (enoxaparin discontinued at INR ≥ 2)
    - apixaban 10 mg orally twice daily for first 7 days, then 5 mg twice daily for 6 months (plus placebo subcutaneous injections and placebo warfarin with sham INR monitoring)
  - primary outcome was composite of recurrent symptomatic venous thromboembolism (VTE) and VTE-related death
  - noninferiority criterion was upper limit of 95% CI < 3.5% for difference between groups in primary outcome
  - 30 patients who did not receive study drugs were excluded from safety analysis
  - comparing apixaban vs. conventional therapy
    - primary outcome in 2.3% vs. 2.7% (95% CI for difference -1.3% to +0.4%, noninferiority met)
    - major bleeding in 0.6% vs. 1.8% (p < 0.001, NNT 84)
    - clinically relevant non-major bleeding in 3.8% vs. 8% (p < 0.05, NNT 24)
    - all-cause death in 1.5% vs. 1.9% (not significant)
    - any serious adverse event in 15.6% vs. 15.2% (no p val reported)
  - Reference - AMPLIFY trial (N Engl J Med 2013 Jul 1 early on editorial can be found in N Engl J Med 2013 Jul 1 early online
- **apixaban may be as effective as low-molecular-weight h urrence of symptomatic deep vein thrombosis (DVT) (level 2 [mid-level] evidence)**
  - based on randomized trial with incomplete blinding
  - 520 patients (mean age 59 years) with DVT randomized MWH plus vitamin K antagonist for 84-91 days
  - LMWH plus vitamin K antagonist group not blinded
  - comparing pooled apixaban groups vs. LMWH plus vitamin K antagonist
    - symptomatic recurrent VTE or asymptomatic deterioration of bilateral compression ultrasound or perfusion lung scan in 4.7% vs. 4.2% (not significant)
    - major or clinically relevant nonmajor bleeding in 7.3% vs. 7.9% (not significant)
  - no significant differences comparing 3 apixaban groups for efficacy or safety outcomes
  - Reference - J Thromb Haemost 2008 Aug;6(8):1313 EBSCO*host* Full Text
- **extended therapy with apixaban reduces risk of recurrent or fatal venous thromboembolism without increasing risk of major bleeding in patients who complete 6-12 months of anticoagulation therapy for venous thromboembolism (level 1 [likely reliable] evidence)**
  - based on randomized trial
  - 2,486 patients with venous thromboembolism (VTE) who completed 6-12 months of anticoagulation therapy were randomized to apixaban (2.5 mg vs. 5 mg) vs. placebo orally twice daily for 12 months
  - all patients were recurrence-free during previous treatment and were eligible for either continuation and cessation of anticoagulation
  - symptomatic recurrent or fatal VTE in
    - 1.7% with apixaban 2.5 mg (p < 0.001 vs. placebo, NNT 14)
    - 1.7% with apixaban 5 mg (p < 0.001 vs. placebo, NNT 14)
    - 8.8% with placebo
  - major bleeding in
    - 0.2% with apixaban 2.5 mg (not significant vs. placebo)
    - 0.1% with apixaban 5 mg (not significant vs. placebo)
    - 0.5% with placebo
  - clinically relevant nonmajor bleeding in
    - 3% with apixaban 2.5 mg (not significant vs. placebo or vs. apixaban 5 mg)
    - 4.2% with apixaban 5 mg (p < 0.05 vs. placebo, NNH 52)
    - 2.3% with placebo
  - Reference - AMPLIFY-EXT trial (N Engl J Med 2013 Feb 21:368(8):699). editorial can be found in N Engl J Med 2013 Feb 21:368(8):767

Evidence quality clearly labeled

Quality limitation explained if evidence downgraded

Internet 100%

Aims - DynaMed and Guideline Developers

DynaMed is collaborating with guideline developers for

- Source for evidence (critically appraised) when developing guideline
- Method to be notified when guidelines warrant updating
- Outlet to disseminate guideline to reach point of care
- Collaboration improves content (both ways)

DynaMed use greatly increased efficiency of high-quality national treatment guideline for breast cancer in Costa Rica

Multiple guideline developers have expressed:

- Desire to use DynaMed for evidence source
- Desire to use GRADE for evidence classification and recommendation classification
- Perception that mapping from SORT to GRADE is difficult

Methods - Mapping SORT to GRADE – round 1

- Perceived concerns to overcome for mapping SORT to GRADE:
  - Explicit level of evidence criteria listed for DynaMed mapped well to Risk of Bias portions of GRADE assessment
  - Precision mapped to “Adequate statistical power”
  - Indirectness, Consistency, and Publication bias were not explicitly stated
  - Criteria to differentiate Moderate-quality from Low-quality evidence were not explicitly stated in listing of Level 2 evidence
- Focus on evidence assessments that would be “key recommendations” for a common topic
- Project started with semi-complicated protocol to map SORT to GRADE and record what additional evidence appraisal was required

Interim Results

- Based on 115 evidence assessments mapped from SORT to GRADE
- Need for additional evidence summarization limited to only 2 instances (both representing needs related to making a recommendation)
  - 1 required identification of a missing direct comparison trial to match desired conclusion for making recommendation
  - 1 required additional harm data to be summarized for evidence with summary limited to efficacy data
- No need for additional critical appraisal
  - 1 item downgraded with explicit attention to publication bias (missed in editing but should have been recognized)
- Realization that level of evidence criterion of "No other factors introducing bias" was being used to capture indirectness, imprecision, inconsistency, and (sometimes) publication bias

Changes to SORT to GRADE mapping protocol

- LOE 1 criteria changed to explicitly include directness, precision, consistency, and no strong suspicion of publication bias

- Level 1 evidence = High-quality evidence
- Level 2 evidence =
  - Moderate-quality evidence for highest-quality study type (e.g., randomized trials) with few limitations, or
  - Low-quality evidence for lower-quality study type (e.g., cohort studies) or for highest-quality study type with many limitations
- Level 3 evidence =
  - Low-quality evidence if indirectness by using surrogate outcomes, or
  - Very low-quality evidence if no comparative evidence

Results - applied to 178 recommendations

- Level 1 evidence = High-quality evidence
  - 31 mapped from 1 to A = High-quality evidence
  - **8 mapped from 1 to B = Moderate-quality evidence**
    - 5 extrapolated focused evidence to broader recommendation
    - 3 had level 1 evidence for some outcomes but level 2 evidence for other outcomes, recommendation considering multiple outcomes
- Level 2 evidence =
  - 99 mapped to B = Moderate-quality evidence
  - 30 mapped to C = Low-quality evidence
- Level 3 evidence =
  - 4 mapped to C = Low-quality evidence due to indirectness
  - 6 mapped to D = Very low-quality evidence

Limits

- This research does not apply to the Recommendations portion of GRADE.
- Multiple instances were found where best current evidence did not match recommendations in current guidelines
- Corollary project - Minimum Criteria for Strong Recommendation
    1. Benefits clearly outweigh harms
    2. Judgment of #1 supported by clinical experts with awareness of current best evidence (quality and quantity)
    3. Clinical domain experts + clinicians representing primary user of recommendation without competing interests
    4. When guideline used for #1-3, recommendation in guideline matches recommendation in DynaMed
    5. Linkages to evidence and guidance considered
    6. If disagreement, need at least 80% agreement with awareness of disagreements (dialog, not simple voting)

Bottom line

- Mapping from DynaMed evidence summaries using SORT to GRADE is much easier than anticipated.
- Guideline developers need to evaluate volume of relevant evidence found in DynaMed, but do not need to be concerned with excessive effort for mapping to GRADE.

For More Information

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