Why GRADE?
Come formulare e come graduare la raccomandazione

Benefit risk assessment, cost/affordability and patients values

Motivi per giungere a una raccomandazione debole

(Motivi per non essere sicuri che i benefici della raccomandazone superino i rischi)

- absence of high quality evidence
- imprecise estimates
- uncertainty or variation in how different individuals value the outcomes
- small net benefits
- uncertainty whether the net benefits are worth the costs (including the costs of implementing the recommendation)

Implicazioni di una raccomandazione forte

- **Patients**: Most people in your situation would want the recommended course of action and only a small proportion would not
- **Clinicians**: Most patients should receive the recommended course of action
- **Policy makers**: The recommendation can be adapted as a policy in most situations

Implications of a weak recommendation

- **Patients**: The majority of people in your situation would want the recommended course of action, but many would not
- **Clinicians**: Be prepared to help patients to make a decision that is consistent with their own values
- **Policy makers**: There is a need for substantial debate and involvement of stakeholders

Come definire la forza della raccomandazione

- No precise threshold for going from a strong to a weak recommendation
- The presence of important concerns about one or more of the above factors make a weak recommendation more likely.
- Panels should consider all of these factors and make the reasons for their judgements explicit.
- Recommendations should specify the perspective that is taken (e.g. individual patient, societal) and which outcomes were considered (including which, if any costs).

Esempi WHO

WHO avian flu guideline 2006

Rec 01: In patients with confirmed or strongly suspected H5N1 infection, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment. Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time. The recommendation applies to adults, including pregnant women and children. Until further information becomes available, the current treatment regimen for H5N1 is as recommended for early treatment of adults, special patient groups (e.g. those with renal insufficiency) and children with *seasonal* influenza.

Schünemann HJ et al. Lancet Infect Dis 2007;7:21-31

WHO PPH Recommendation:

In the absence of active management of the third stage of labour, a uterotonic drug (oxytocin or misoprostol) should be offered by a health worker trained in its use for prevention of PPH. (*Strong recommendation, moderate quality evidence*)

- Remarks:

For misoprostol, this recommendation places a high value on the potential benefits of avoiding PPH and ease of administration of an oral drug in settings where other care is not available, but notes there is only one study. The only trial relevant to this recommendation used 600 mcg of misoprostol. The efficacy of lower doses has not been evaluated. There is still uncertainty about the lowest effective dose and optimal route of administration.

WHO PPH Recommendation:

In the context of active management of the third stage of labour, if all injectable uterotonic drugs are available:

Skilled attendants should offer oxytocin to all women for prevention of PPH in preference to ergometrine/methylergometrine. (*Strong recommendation, low quality evidence*)

If oxytocin is not available:

Skilled attendants should offer ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine to women without hypertension or heart disease for prevention of PPH. (*Strong recommendation, low quality evidence*)

- Remarks:

These recommendations place a high value on avoiding adverse effects of ergometrine and assume similar benefit for oxytocin and ergometrine for preventing PPH.

Esempi da Antithrombotic therapy

Chest 2008

The Primary and Secondary Prevention of Coronary Artery Disease*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Richard C. Becker, MD; Thomas W. Meade, DM, FCCP; Peter B. Berger, MD; Michael Ezekowitz, MD; Christopher M. O'Connor, MD; David A. Vorchheimer, MD; Gordon H. Guyatt, MD, FCCP; Daniel B. Mark, MD; and Robert A. Harrington, MD, FCCP

La raccomandazione

Recommendations

5.0. For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of a cardiac event of > 10%), we recommend 75–100 mg aspirin daily over either no antithrombotic therapy or VKA (Grade 2A).

5.1. For patients at particularly high risk of events in whom INR can be monitored without difficulty, we suggest low-dose VKA with a target INR of approximately 1.5 over aspirin therapy (Grade 2A).

5.3. For all patients, we recommend against the routine addition of clopidogrel to aspirin therapy in primary prevention (Grade 1A). **For patients with an aspirin allergy who are at moderate to high risk for a cardiovascular event, we recommend monotherapy with clopidogrel** (Grade 1B).

La raccomandazione

5.4. For women < 65 years of age who are at risk for an ischemic stroke, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2A).
5.4.1. For women > 65 years of age at risk for ischemic stroke or MI, and in whom the concomitant risk of major bleeding is low, we suggest aspirin at a dose of 75–100 mg/d over no aspirin therapy (Grade 2B).

La spiegazione

Values and preferences: The recommendation of aspirin over VKA places a relatively low value on a small absolute reduction in coronary events and deaths and a relatively high value on avoiding the inconvenience, cost, and minor bleeding risk associated with oral VKA. The low target INR value required in primary prevention typically mandates less frequent monitoring; on average every 2 to 3 months and is associated with lower risk of bleeding.

Patients, particularly those in the highest risk groups for whom systems permitting meticulous monitoring of anticoagulant therapy are available, who place a relatively high value on small absolute risk reductions in coronary events and are not influenced by an element of inconvenience and potential bleeding risk associated with VKA are likely to derive the greatest overall benefit from administration of VKA rather than aspirin.

3.1 Elastic Stockings and Compression Bandages To Prevent Postthrombotic Syndrome

3.1.1. For a patient who has had a symptomatic proximal DVT, we recommend the use of an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg if feasible (Grade 1A)**. Compression therapy, which may include use of bandages acutely, should be started as soon as feasible after starting anticoagulant therapy and should be continued for a minimum of 2 years, and longer if patients have symptoms of the postthrombotic syndrome (PTS). (Note: feasibility, both short and long term, refers to ability of patients and their caregivers to apply and remove stockings.)**

Underlying values and preferences: This recommendation attaches a relatively high value to long-term prevention of the postthrombotic syndrome (PTS) and a low value to the burden (*eg*, inconvenience or discomfort) associated with wearing stockings.

Strong- we reccommend
weak – we suggest
una modesta differenza?

3.3 Knee Arthroscopy

3.3.1. For patients undergoing knee arthroscopy who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use thromboprophylaxis other than early mobilization (Grade 2B).

3.3.2. For patients undergoing arthroscopic knee surgery who have additional thromboembolic risk factors or following a complicated procedure, we recommend thromboprophylaxis with LMWH (Grade 1B).

Un passaggio importante: valori e preferenze del pz

Our main strategy for dealing with this unsatisfactory situation is to make the values and preferences underlying the recommendations explicit whenever the panelists believed that value and preference issues were crucial for a recommendation. For example, Albers et al[11] suggest for patients with acute ischemic stroke of > 3 h but < 4.5 h that clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA (Grade 1A). The authors noted in the corresponding values and preferences statement, "This recommendation assumes a relatively low value on small increases in long-term functional improvement, a relatively high value on avoiding acute intracranial hemorrhage and death, and a relatively high degree of risk aversion."