Applying GRADE Method to Solve the Issue of Composite Endpoints for Stable Angina

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Review on MACE definition (I)

- Cardiovascular trials and reviews commonly use Major Adverse Cardiac Events (MACEs) as one of their primary final endpoints.
  - » composite endpoint
  - » there are different definitions adopted by different organizations, professional associations and guidelines producers.
- **Objective**
  - » To perform a review of existing definitions on MACE
  - » To agree a standardized and common definition that could be useful for those with the same PICO question

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Review on MACE definition (II)

- We carried out a systematic review of studies that included stable angina (in its broad definition including stable chest pain/discomfort) in the Patients PICO question (**P**atients, **I**ntervention or **E**xposure, **C**omparison and **O**utcomes) and considered MACE as primary or secondary final outcome.
- We used a highly sensitive search strategy, with no restriction on study type or language, but English, German, Spanish, Italian, French or Portuguese.
- We finally excluded case series and individual reports. We searched MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials and Systematic Reviews.
- Auto-alerts were run in MEDLINE and EMBASE from May 2008 to June 2015.

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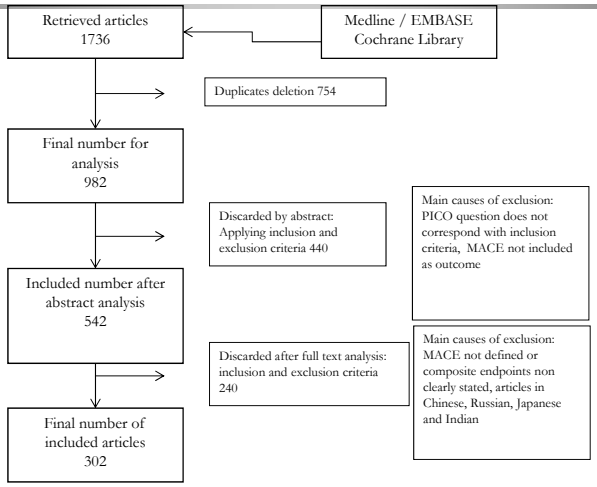
Search flow-chart



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Some MACE definitions

Major adverse cardiac events (MACE) defined as cardiac death, nonfatal myocardial infarction, or target lesion revascularization.	**Capodano et al. Circulation: Cardiovascular Interventions. 2009; 2: 302-308**
MACE: Major adverse cardiac events is defined as all-cause death, MI, and any repeat coronary revascularization as adjudicated by the adverse clinical event committee.	Fearon WF, Tonino PA, De Bruyne B, Siebert U, Pijls NH; 2007
MACE. Major adverse cardiac events were defined as a composite of death, myocardial infarction, and any repeat revascularization.	Tonino PA, De Bruyne B, Pijls NH, et al; N Engl J Med. 2009 Jan 15;360(3):213-24.
MACEs, defined as death, myocardial infarction, and late revascularization.	Nakazato R, Arsanjani R, Achenbach S, et al. 2014
Most include MI, stroke, and death; others include rehospitalization for heart failure, revascularization, cardiac arrest, or bleeding complications.	Myles PS. 2014
MACE [composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or target-lesion revascularisation]	Mehran R, Baber U, Steg PG, et al. Lancet. 2013.
MACE, defined as the composite of cardiac death, myocardial infarction [MI], and target vessel revascularisation [TVR]	Zhang F, Ge J, Qian J, Ge L, Zhou J; 2014.
Major cardiac event (heart attack, angina, stroke or heart failure) or underwent revascularization	American Heart Association, 2014
MACE: myocardial infarction (MI), cerebrovascular accident (CVA), emergency revascularisation or cardiac related death	NICE, 2012
Major adverse cardiovascular events were defined as cardiac death, acute myocardial infarction (AMI), and stent thrombosis and target lesion revascularization	Naseem M, Samir S 2014
MACE: CV death, non fatal MI, unstable angina, heart failure, stroke, other CV events	Ogawa H et al.; 2013

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Single endpoints included in MACE for stable angina

Table Frequency of individual endpoints included in MACE definition in the retrieved references.

Individual endpoints included in MACE	Number of studies (%)
Cardiovascular death	105 (34.7)
Death of any cause	155 (51.3)
Non fatal MI	279 (92.4)
Non fatal stroke	102 (33.8)
Revascularization	211 (69.9)
Hospitalization for unstable angina	35 (11.6)
Major bleeding	5 (1.7)
Minor bleeding	1 (0.3)
others	127 (42.1)

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Most frequent combinations for stable angina

Most common combinations of MACE	Number of studies (%)
Non fatal MI + revascularization	186 (61.6)
Death of any cause + non fatal MI + revascularization	111 (36.8)
Cardiovascular death + non fatal MI + revascularization	92 (30.5)
Death of any cause + non fatal MI + revascularization + stroke	56 (18.5)
Death of any cause + non fatal MI + stroke	48 (15.9)
Cardiovascular death + non fatal MI + stroke	47 (15.6)

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In our case…

- MACE is used as primary or secondary outcome without any discussion on why this decision was taken.
- Most of the retrieved references included MACE as outcome and some of them did not define which individual outcomes were encompassed under MACE umbrella
- The most common combination of individual endpoints was non-fatal myocardial infarction and revascularization. Nevertheless, this combination may address a concrete research question while some others could remain not well answered.
- It is important to establish the follow-up periods that lead to achieve these considered important outcomes. In some of the retrieved articles the follow-up periods were the same for all the individual outcomes
- There is no common MACE definition and this heterogeneous inclusion of individual outcomes and follow up periods could respond to the differences in the research questions of individual studies.

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A possible solution

1+1=¡uff!

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The GRADE framework and the selection of the outcomes of interest

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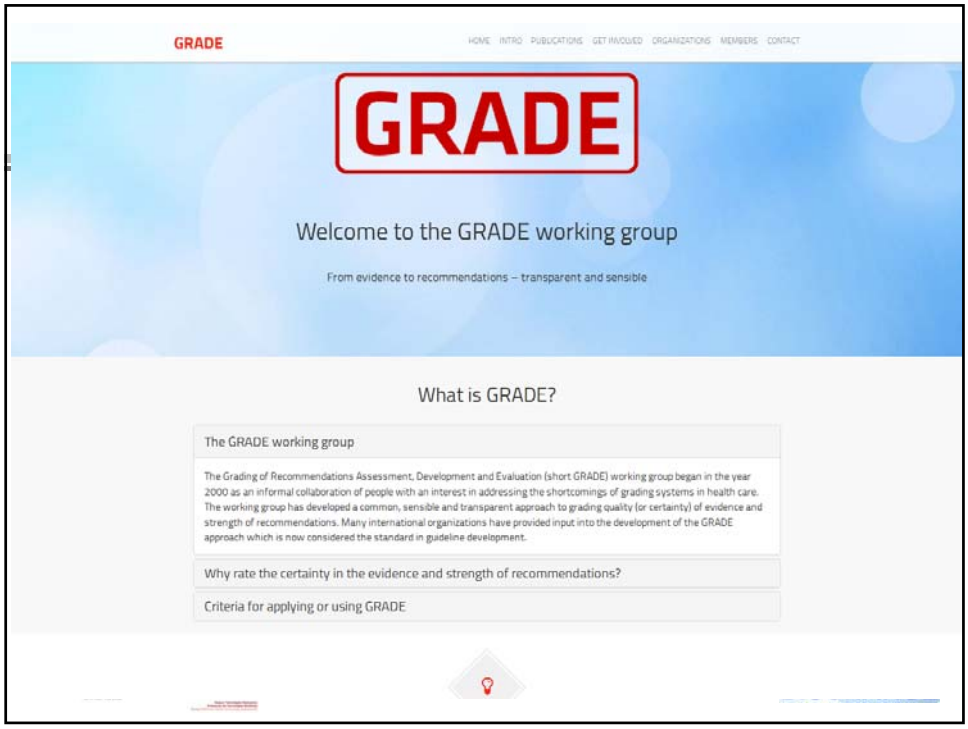
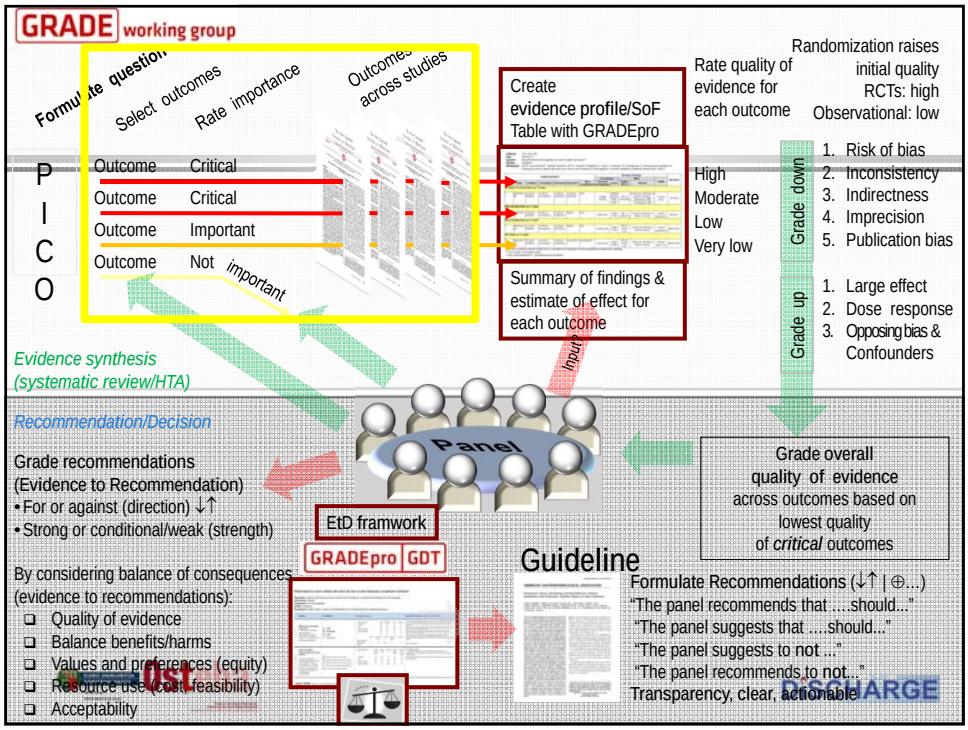

GRADE
HOME INTRO PUBLICATIONS GET INVOLVED ORGANIZATIONS MEMBERS CONTACT
GRADE
Welcome to the GRADE working group
From evidence to recommendations – transparent and sensible
What is GRADE?
The GRADE working group
The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations. Many international organizations have provided input into the development of the GRADE approach which is now considered the standard in guideline development.
Why rate the certainty in the evidence and strength of recommendations?
Criteria for applying or using GRADE


GRADE working group
Formulate question
Select outcomes
Rate importance
Outcomes across studies
P
I
C
O
Outcome Critical
Outcome Critical
Outcome Important
Outcome Not important
Create evidence profile/SoF Table with GRADEpro
Rate quality of evidence for each outcome
Randomization raises initial quality
RCTs: high
Observational: low
High
Moderate
Low
Very low
Grade down
1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias
Grade up
1. Large effect
2. Dose response
3. Opposing bias & Confounders
Summary of findings & estimate of effect for each outcome
Input?
Evidence synthesis (systematic review/HTA)
Recommendation/Decision
Panel
Grade overall quality of evidence across outcomes based on lowest quality of critical outcomes
Grade recommendations (Evidence to Recommendation)
• For or against (direction) ↓↑
• Strong or conditional/weak (strength)
By considering balance of consequences (evidence to recommendations):
Quality of evidence
Balance benefits/harms
Values and preferences (equity)
Resource use (cost, feasibility)
Acceptability
EtD framwork
GRADEpro GDT
Guideline
Formulate Recommendations (↓↑ | ⊕...)
"The panel recommends that ....should..."
"The panel suggests that ....should..."
"The panel suggests to not ..."
"The panel recommends to not..."
Transparency, clear, actionable
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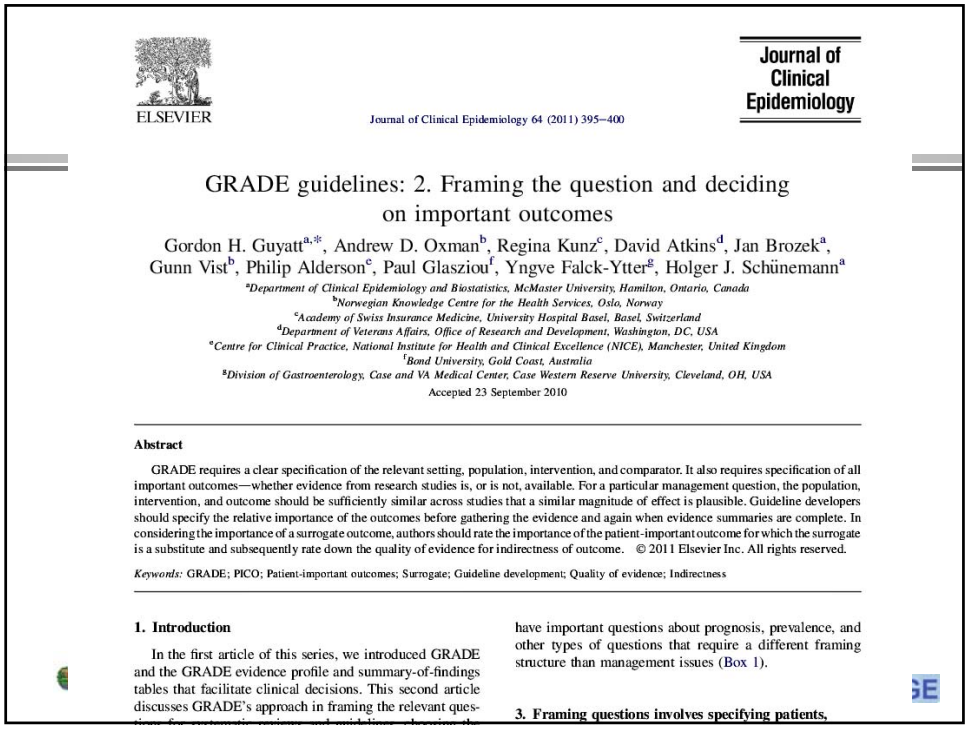

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GRADE guidelines: 2. Framing the question and deciding on important outcomes

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Abstract

GRADE requires a clear specification of the relevant setting, population, intervention, and comparator. It also requires specification of all important outcomes—whether evidence from research studies is, or is not, available. For a particular management question, the population, intervention, and outcome should be sufficiently similar across studies that a similar magnitude of effect is plausible. Guideline developers should specify the relative importance of the outcomes before gathering the evidence and again when evidence summaries are complete. In considering the importance of a surrogate outcome, authors should rate the importance of the patient-important outcome for which the surrogate is a substitute and subsequently rate down the quality of evidence for indirectness of outcome.

Keywords: GRADE; PICO; Patient-important outcomes; Surrogate; Guideline development; Quality of evidence; Indirectness

1. Introduction

In the first article of this series, we introduced GRADE and the GRADE evidence profile and summary-of-findings tables that facilitate clinical decisions. This second article discusses GRADE's approach in framing the relevant ques-

have important questions about prognosis, prevalence, and other types of questions that require a different framing structure than management issues (Box 1).

3. Framing questions involves specifying patients,

Outcomes classification

- ✓ Those using GRADE for guideline development will make a preliminary classification of outcomes into those that are **critical**, those that are **important but not critical**, and those of **limited importance**. The first two classes of evidence will bear on guideline recommendations; the third may or may not.
- ✓ Guideline developers may choose to **rate outcomes** numerically on a **1–9 scale** (7–9, critical; 4–6, important; and 1–3, of limited importance) to distinguish between importance categories .

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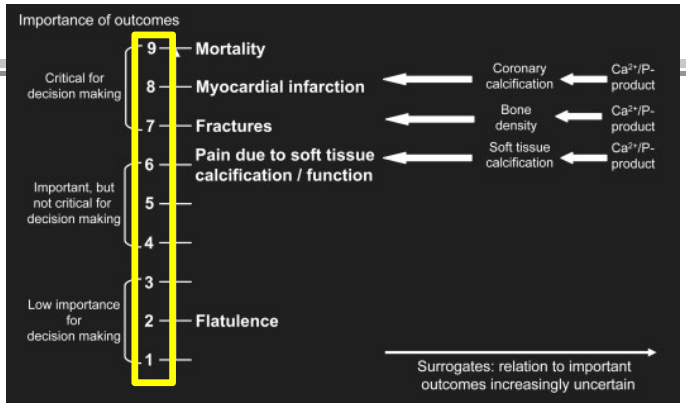

Fig. 1
Hierarchy of outcomes according to their importance to assess the effect of phosphate-lowering drugs in patients with renal failure and hyperphosphatemia.

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Outcomes classification

- ✓ **Ranking outcomes by their relative importance** can help to focus attention on those outcomes that are considered most important and help to resolve or clarify disagreements.
- ✓ **Decisions** regarding the overall quality of evidence supporting a recommendation may **depend on which outcomes are designated as critical** for making the decision (e.g., those rated 7, 8, or 9, on the 9-point scale mentioned earlier) and which are not.

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Surrogate outcomes

- Guideline panel addressing “the use of novel agents to lower phosphate in patients with renal failure and hyperphosphatemia”.
  - What are the intended effects of the intervention?
    - The obvious answer: lower serum phosphate
    - More appropriate answer: to reduce mortality, myocardial infarction, fractures, and pain because of soft-tissue calcification.
- Guideline developers should consider surrogate outcomes only when high-quality evidence regarding important outcomes is lacking.

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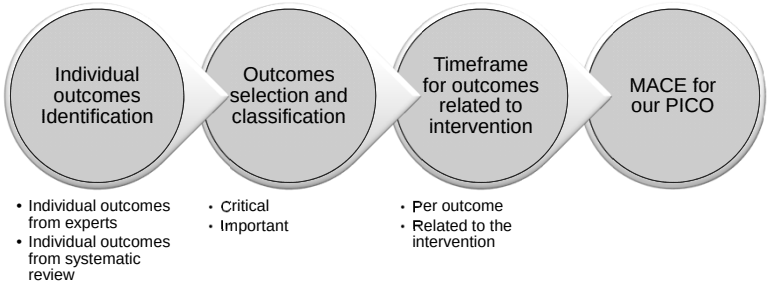
What do we propose



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Thank you for your attention

Any questions?