

**Osteba, Basque Office for HTA  
Ministry for Health  
Basque Country**

**DISCHARGE  
WP08**

**“Systematic Review of Evidence”**



# Contact Details WP08

## “Systematic review”

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**DISCHARGE**

# Overview

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- | There are existing Clinical Practice Guidelines (CPG)76-77 and meta-analyses on the role of CT in the management of patients with stable angina pectoris.
  - » Systematic process include data on new clinical (pragmatic randomised trials), gender, quality of life and economic evidences
- | Osteba will integrate those evidences in recommendations to be followed at the different levels of decision from clinical practice to coverage.
- | Role of EUnetHTA core model and GRADE methods could play

# Objectives

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1. To define the questions and the scope of the systematic review
2. To perform a systematic review of existing evidence
3. To incorporate the data evolving from the PRCT, gender, economic and quality of life (QoL) analysis (by means of EUnetHTA core model and Mini-HTA methodology)
4. To establish recommendations for practice and coverage decisions

# What we have done so far...

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- | Questions definition according to PICO system
  - » D8.1
- | Systematic review of current evidence
  - » D8.2
- | Analysis of MACE definition
  - » Composite result
  - » Different interpretations

# D8.1 Questions' definition

<b>P</b> atients	<b>I</b> ntervention	<b>C</b> omparison	<b>O</b> utcomes
Patients with stable chest pain and intermediate pretest likelihood of CAD.	CT scan	Invasive coronary angiography	Major adverse cardiac events (MACE)
Patients with stable chest pain and intermediate pretest likelihood of CAD.	CT-scan	None	Diagnostic value Prognostic value
Patients with stable chest pain and intermediate pretest likelihood of CAD.	CT scan	None	Cost-effectiveness

# D8.2 Search results

## | Search results in major databases:



| 73 articles and reports were retrieved from major databases. They were filtrated and analyzed accordingly.

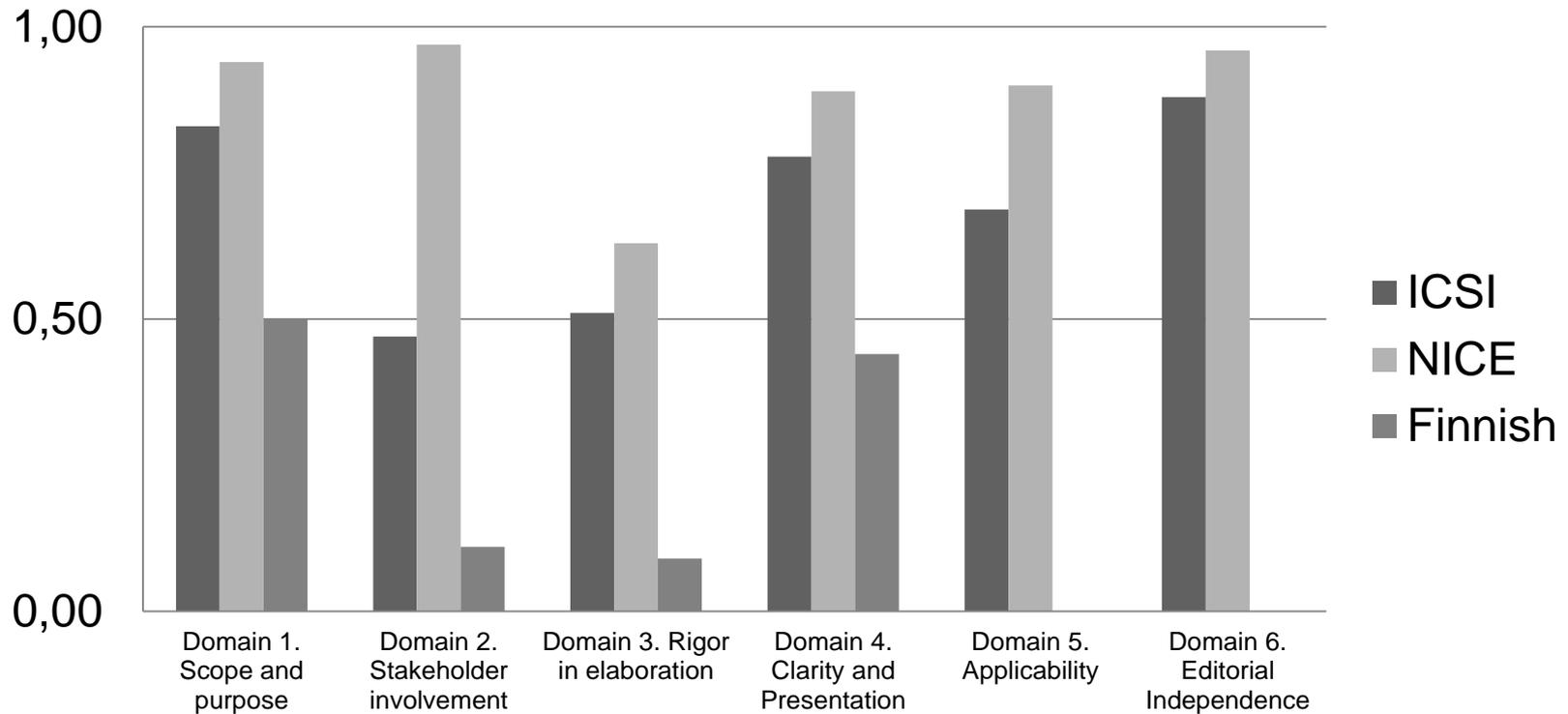
# Guidelines

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- | 14 retrieved
- | 10 excluded
- | 4 finally considered
  - » Evaluated according to quality characteristics

# Guidelines analysis AGREE II

## Guidelines evaluation



# Main conclusions from guidelines

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- I Currently available guidelines on risk assessment by imaging contain differing recommendations. This is due to the lack of evidence in some of the areas of interest, which generates that the recommendations are mostly based on consensus in these areas or on low quality evidence.

» More research, including randomized controlled trials, evaluating the impact of imaging on clinical final outcomes and costs is needed. This issue is aligned with a previously made analysis published in 2011 on Imaging of Asymptomatic Coronary Artery Disease (Ferket et al, 2011).

- I One of the best scored guidelines (NICE, 2010) that scored more than 80 in most of the domains, included the following research question:

» “Further research should be undertaken to evaluate the clinical and cost effectiveness of multislice CT coronary angiography compared with functional testing in the diagnosis of angina in a population of people with stable chest pain who have a moderate (30–60%) likelihood of CAD.”

# Main conclusions on diagnosis and prognostic value

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- | Three trials explored the diagnostic value of CCTA in ED (Goldstein et al, 2010; Hoffman et al, 2012; Litt et al, 2012) concluding that:
  - » the use of CT coronary angiography in groups of low to intermediate risk has shown to be an efficient, effective and safe method
- | Cho et al 2012 in an observational study found that
  - » In patients with suspected coronary artery disease, coronary CTA discriminates future risk of MACE in patients independent of XECG results.
  - » Compared with coronary CTA, XECG has an additive prognostic value **only in patients with moderate to severe stenosis on coronary CTA.**

# Main conclusions on cost-effectiveness

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- | In light of further evidence in favor of CCTA, these recommendations need reevaluation.
  - » all the economic models included in the latest SR were based on intermediate results and non-randomized observational studies.
  - » the **need for a well designed randomized controlled trial** with a record of final outcomes on morbidity and mortality seemed to be crucial **to determine the effectiveness, prognostic value and cost-effectiveness** of CCTA in comparison to other more invasive imaging alternatives like coronary arteriography.

# Review on MACE definition (I)

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- | 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 used in the project

# Review on MACE definition (II)

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- | A literature search was performed in the major databases as stated before: Medline, EMBASE.
- | Webpages of the main guidelines producers and professional associations as follows:
  - » AHA. American Heart Association <http://www.heart.org>
  - » American College of Radiology <http://www.acr.org>
  - » European Society of Cardiology <http://www.escardio.org/>
  - » NHMRC. National Health and Medical Research Council. <https://www.nhmrc.gov.au/guidelines-publications>
  - » NICE. <http://www.nice.org.uk>
  - » Royal College of Physicians of London. <http://www.rcplondon.ac.uk/>
  - » SIGN. <http://www.sign.ac.uk>

# Some MACE definitions

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

# MAJOR CONCLUSIONS

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- | There is no standard definition for MACE
- | It is considered as a composite end-point.
- | There are several organizations that consider MACE only for cardiac origin events while others include death of any origin as a possible part of the composite endpoint.
- | Stroke or cerebrovascular accidents were included in some of the definitions while others disregard the inclusion of this.

# In fact...

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- | **Myles, 2014**

- | “Cardiovascular trials commonly use major adverse cardiac events (MACEs) as a composite primary endpoint. However, **there is no standard definition for MACE**. Most include MI, stroke, and death; others include rehospitalization for heart failure, revascularization, cardiac arrest, or bleeding complications.
- | An influential trial in noncardiac surgery found that perioperative beta-blockers reduced the risk of MI but increased the risk of stroke and death. Such conflicting findings challenge the veracity of such composite endpoints and raise a far more important question: which of these endpoints, or even others that were unmeasured, are most important to a patient recovering from surgery? Given the primary aims of cardiac surgery are to relieve symptoms and improve good quality survival, it is disability-free survival that is the ultimate outcome measure.”

# Recommendation

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- | To adopt an agreed definition by the members of the project on the basis of the systematic review and currently used variables
- | To establish a committee to resolve possible doubts on the occurrence of a MACE and establish same criteria in all the clinical sites

# RATIONALE

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- | The last systematic review on MACE was published in 2008 and included mostly RCTs.
- | Our systematic review was based on the statements by the scientific societies, the CPGs producers and systematic reviews.
  - » **ACTION:** to extent our review from 2007 to 2014 and RCTs.
- | Identify the individual outcomes that are allotted to the different MACE definitions and to analyze them individually.
  - » **ACTION:** to develop a table of the different MACE definitions and the individual outcomes they include.

# METHOD

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- | GRADE method for the definition of critical and major variables
- | Systematic review of outcomes used in MACE definitions
  - » Guidelines
  - » Trials (Last SR finished its search in 2007)
  - » Extend the search up to 2014
- | Design a survey with the variables identified and send to the project mailing list (clinical sites).
  - » Results will be electronically recorded and pooled



TO MACE OR NOT TO MACE, THAT'S THE QUESTION...

**THANKS**