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CE - METHODOLOGICAL NOTES

When should we change our clinical practice based on the results of a clinical study? Study endpoints

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Introduction

We are now familiar with the three-leaf clover of the evidence and we know what is the most appropriate study design for answering clinical questions regarding diagnosis, prognosis or intervention [1, 2]. It is time to read carefully a clinical study and decide if we shall change our clinical practice following the study's results. One of the first things to look at are the declared endpoints.

The majority of studies address several clinical questions at one time, but only one has to be the main objective of the study, while the others are just ancillary. Thus, we will have primary and secondary outcomes (Table 1).

Primary and secondary outcomes

The *primary outcome* (or endpoint) is the main feature for which the groups under study are compared. It represents the translation of the original clinical question underlying the study into a quantitative variable. The identification of the primary endpoint has some relevant implications. First, the "success" of the study depends on the demonstration that this outcome is different between the study groups. In addition, the design of the study must be based on the chosen primary endpoint. In particular, the number of patients to be included in the study (the *sample size*) has to be calculated considering only the primary outcome. Therefore, the study is powered to detect differences only in the main objective. The endpoints other than the primary are termed *secondary outcomes*. There are usually several secondary endpoints in a clinical study. This is the reason why the findings based on secondary outcomes, even if statistically significant, are not strong enough to support changes in clinical practice, as their statistical significance might be due to the effect of chance. Indeed, when several secondary endpoints are considered, the risk of observing a significant result only by chance is increased well over the usual nominal $\alpha = 5\ \%$. Hence, the results provided by secondary analyses must be considered just as explorative, as they need to be confirmed in subsequent studies in which the statistically significant secondary endpoint will be promoted to primary. In conclusion, we could summarize as "one study, one primary endpoint". Thus, only primary outcome results could contribute to change our clinical practice.

Clinically meaningful ('hard') and surrogate ('soft') outcomes

Primary and secondary outcomes can also be classified according to their relevance for the patients.

For example, mortality, stroke or myocardial infarction occurrence are without any doubts highly relevant outcomes, whereas the reduction of cholesterol level, arterial pressure or heart rate are less relevant, as they might be not related to an improved survival. *Clinically meaningful* (or 'hard', or 'patient oriented') *outcomes* are all those endpoints that are directly relevant to the patient.

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Table 1 Classification of outcomes

Classification	Definition	Conclusions
According to the aim of the study		
Primary outcome	The outcome of greatest importance	Might change clinical practice.
Secondary outcomes	All the additional outcomes considered in a clinical study	Only "explorative" purposes. Not suitable for changing clinical practice
According to the relevance for the patient		
Hard (patient oriented, clinically meaningful)	Outcomes directly relevant to the patient	Might change clinical practice
Soft (surrogate)	Outcomes not directly relevant to the patient, but supposed to be related to a more clinically relevant outcome	Only "explorative" purposes. Not suitable for changing clinical practice

Nevertheless, sometimes researchers perform studies selecting as primary an outcome that is not 'hard'. In 2011, DeFronzo et al. [3] reported the results of a clinical trial which assessed the effect of pioglitazone in the prevention of diabetes. The primary endpoint was the development of diabetes in patients with impaired glucose tolerance. Is this outcome important enough to lead to a change in clinical practice? Development of diabetes is without doubts less important to patients than mortality or some other 'hard' events. The rationale of considering development of diabetes as a primary endpoint is that it is supposed to be related to death or stroke.

A *surrogate* (or 'soft') *outcome* is a patient's characteristic that is measured in substitution of a more clinically relevant one (e.g., death, stroke, myocardial infarction) and that is expected to correlate well with clinically relevant outcomes. Usually a surrogate endpoint occurs in a shorter time, it is easier to assess and it is more frequent than a clinically relevant one. These characteristics ensure that a clinical study can be conducted in a shorter time frame, thus leading to a faster clinical answer while requiring a smaller number of patients (as the events are more frequent) and finally reducing the overall costs of the study. For these reasons, surrogate outcomes are often used and appealing to clinical researchers and to industry. Nevertheless, sometimes it might happen that improvements in surrogate endpoints do not result in improvement of clinically meaningful endpoints. A well-known example is represented by the CAPS study demonstrating that some drugs' prophylaxis reduced ventricular arrhythmia in patients with acute myocardial infarction (AMI) [4].

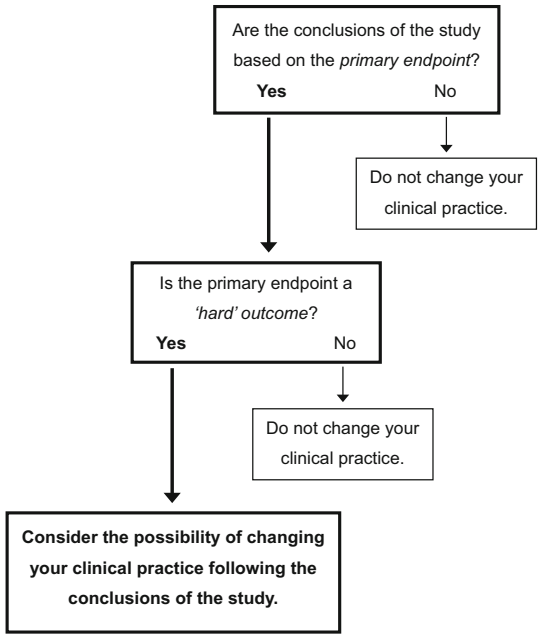

Fig. 1 When to change clinical practice

Based on these findings, many patients had then been treated with antiarrhythmic drugs after an AMI, until a subsequent trial did confirm that they reduced arrhythmia but increased mortality [5]. This example underlines how taking clinical decision based on trials considering surrogate endpoints can be very dangerous.

Conclusions

In conclusion, we shall not change our clinical practice unless a *hard primary endpoint* of the study has been shown to be significant (Fig. 1). All the others statistically significant results reported in a study should be considered just as "explorative" findings. However, in the next series, we will draw your attention on some pitfalls, that must be considered even in the case of a study with a significant hard primary endpoint.

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with human and animals performed by any of the authors.

Informed consent For this type of study formal informed consent is not required.

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