Clinical Trials and Clinical Practice in the Real World. Do We Know Why Efficacy Is Confused With Effectiveness?

To the Editor:

We have read with great interest the general results of the MASCARA study[1] and the accompanying editorial[2] both recently published in the Revista Española de Cardiología.

The MASCARA study defined itself as a study of effectiveness,[3] and not of efficacy, within the management of acute coronary syndrome (ACS) in Spain in 2004-2005. Although the determination of the real benefit of primary percutaneous coronary intervention in ST-elevation acute coronary syndrome and an early invasive strategy in the first 48 hours of non-ST-elevation acute coronary syndrome were among the objectives, this proved impossible to achieve when analyzing the results of the study,[1] although the authors note in the conclusions that there has been an increase in invasive strategies in Spain compared to previous studies.

Although the "theoretical" aims of the MASCARA study were not fulfilled, the results presented, in our opinion, are very interesting from the scientific standpoint and contribute interesting reflections on cardiological practice in a time of ever-changing information. Although the differences between randomized studies and registries are well known[2] to all the professionals involved in the treatment of ACS patients, we would like to see, in registries as well designed as this, that the outcomes of strategies with clear scientific support—primary percutaneous

coronary intervention and early intervention—produce clear clinical improvement "in the real world" as have other recent interventions, such as the use of beta-blockers in heart failure.[4]

The conclusions of the MASCARA study refer to factors related to the healthcare process that impede the implementation of strategies that have clearly demonstrated benefit in cardiovascular medicine. We should investigate this field further, and analyze the causes of discrepancies between clinical trials and the "real world"—where many of the problems that prevent us providing our patients with better treatment are located—in order to reduce the leading cause of death in our society, cardiovascular disease. These various related factors, some known and others unknown, are the confounding factors that prevent us from transforming efficacy into effectiveness. There is a striking lack of studies on various prevalent diseases, such as the MASCARA study, that report the actual situation regarding these diseases in "the real world."

There are economic reasons for the lack of resources from the public and private sectors which are naturally more interested in demonstrating prognostic improvement, albeit marginal, and in groups scarcely representative of daily clinical practice. Similarly, we also do not know if the benefits of various pharmacological therapies overlap with others, are complementary or only benefit various risk groups (concomitant use of anti-IIb/IIIa, early and dual antiplatelet therapy at various doses for the management of non-ST-elevation acute coronary syndrome), or if, on the other hand, they could cause adverse effects unacceptable in "the real world" (for example, bleeding or hyperkalemia). Health infrastructures can make it unviable to apply various treatments (for example, due to the ambulance system in specific geographic areas).

However, many problems arise in the scientific literature regarding the identification of these associated clinical factors, that is, the factors that confound efficacy with effectiveness. Today, the available scientific information in many cases emphasizes statistically significant differences, although small, obtained from combined outcome variables of debatable clinical relevance. This is done even by analyzing substudies—with their known methodological biases[5]—of major clinical trials of cardiovascular therapy. Furthermore, scientific meetings and congresses also focus on therapies that show marginal benefits in groups of highly selected patients that scarcely reflect daily clinical reality.

In short, the striking data reported by the MASCARA study once again highlights the relevance of clinical factors related to patient management, that is, the factors confounding efficacy with effectiveness. We should increase our knowledge concerning these factors in order to be able to control them and make efficacy a synonym of effectiveness.

Manuel F. Jiménez-Navarro, Fernando Cabrera-Bueno, Antonio J. Muñoz-García, and Eduardo de Teresa-Galván

Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain.

REFERENCES

1. Ferreira-González I, Permanyer-Miralda G, Marrugat J, Heras M, Cuñat J, Civiera E, et al. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. Rev Esp Cardiol. 2008;61:803-16.
2. Cequier A. El registro MASCARA desenmascara la realidad asistencial del manejo de los síndromes coronarios agudos en España. Rev Esp Cardiol. 2008;61:793-6.
3. Permanyer-Miralda G, Ferreira-González I, Marrugat DL, Bueno-Zamora H. Bases conceptuales y metodológicas del estudio MASCARA: el reto de la efectividad. Med Clin (Barc). 2005;125:580-4.
4. Jost A, Rauch B, Hochadel M, Winkler R, Schneider S, Jacobs M, HELUMA study group. Beta-blocker treatment of chronic systolic heart failure improves prognosis even in patients meeting one or more exclusion criteria of the MERIT-HF study. Eur Heart J. 2005;26:2689-97.
5. Alfonso F, Segovia J, Heras M, Bermejo J. Publicación de ensayos clínicos en revistas: consideraciones editoriales. Rev Esp Cardiol. 2006;59:1206-14.

Response

To the Editor:

We thank Jiménez-Navarro et al for their letter and we can only agree with their comments. In relation to our study,[1] the authors refer to the relevance of knowing the outcomes of healthcare in real clinical practice. While agreeing with this, we want to highlight some aspects regarding the interpretation of our study that illustrate the complexity of interpreting observational studies. These difficulties have to be added to those already mentioned by Jiménez-Navarro et al.

The MASCARA study shows that, during 2004-2005, invasive procedures in acute coronary syndromes in the participating hospitals were not associated with evident clinical benefit. While this datum seems barely debatable, its interpretation is open to speculation. Compared to previous Spanish registries (PRIAMHO II[2] and DESCARTES[3]), the MASCARA study found a striking increase in the use

of drugs and percutaneous coronary intervention, and it can be assumed that this represents an important change in healthcare practice over a short period. We could form the hypothesis that the process that would have enabled good outcomes (prehospital and hospital waiting periods, correct patient selection,[4] etc) would have been highly complex; even with a certainly appropriate technical execution of the intervention, the whole process would not have been sufficiently well-developed by 2004-2005. The message of this interpretation would be that to implement the invasive procedures recommended in the guidelines would not only mean carrying these out, but also appropriately modifying the healthcare management process. Our study could be a useful reference point for each center to assess to what extent this is the case at present.

On the other hand, the quality requirements that a valid registry should have are far less established than those for clinical trials, which can further hinder correct interpretation. The difficulties involved in registries that accurately reflect the situation of the participating centers are usually underestimated and barely recognized in the studies. The MASCARA study necessarily involved complex quality control that excluded 18 centers to ensure the validity of the results obtained. It is far from easy to ensure consecutive and complete inclusion in the current conditions of hospital practice. And in its absence, the resulting biases can be surprisingly high.[5]

These observations serve to illustrate the complexity involved in conducting and interpreting observational studies, the need for which Jiménez-Navarro et al make very clear.

Cayetano Permanyer Miralda
and Ignacio Ferreira González

Unidad de Epidemiología, Servicio de Cardiología, Hospital Vall d'Hebron, Barcelona, Spain

REFERENCES

1. Ferreira-González I, Permanyer-Miralda G, Marrugat J, Heras M, Cuñat J, Civeira E, et al. Estudio MASCARA (Manejo del Síndrome Coronario Agudo. Registro Actualizado). Resultados globales. Rev Esp Cardiol. 2008;61:803-16.
2. Arós F, Cuñat J, Loma-Osorio A, Torrado E, Bosch X, Rodríguez JJ, et al. Tratamiento del infarto agudo de miocardio en España en el año 2000. El estudio PRIAMHO II. Rev Esp Cardiol. 2003;56:1165-73.
3. Bueno H, Bardají A, Fernández-Ortiz A, Marrugat J, Martí H, Heras M. Manejo del síndrome coronario agudo sin elevación del segmento ST en España. Estudio DESCARTES (Descripción del Estado de los Síndromes Coronarios Agudos en un Registro Temporal Español). Rev Esp Cardiol. 2005;58:244-52.
4. Ferreira-González I, Permanyer-Miralda G, Heras M, Cuñat J, Civeira E, Arós F, et al. Patterns of use and effectiveness of early invasive strategy in non–ST-segment elevation acute coronary syndromes: An assessment by propensity score. Am Heart J. 2008;156:946-53.
5. Ferreira-Gonzalez I, Marsal JR, Ribera A, Cascant P, Marrugat J, Bueno H, et al. Registries in coronary artery disease: assessing or biasing real world data? Circulation. 2008;118 Suppl 2:1162.