

The EPICOR Study: What Does It Tell Us About Acute Coronary Syndrome in Argentina?

Estudio EPICOR: ¿Qué nos dice sobre el síndrome coronario agudo en Argentina?

XAVIER ROSSELLO, MD, PHD,^{1, 2} HÉCTOR BUENO, MD, PHD,^{1, 2, 3, 4}

There is limited information on long-term antithrombotic patterns of use in patients with acute coronary syndrome (ACS) since the recent advent of the last generation of antithrombotic drugs, including ticagrelor and prasugrel. Independently of randomized clinical trials, observational studies are necessary to accurately establish what is occurring in daily clinical practice. The evidence obtained from clinical trials is clear: antiplatelet agents improve the prognosis of patients with ACS at the expense of increasing bleeding risk, (1-7) but to what extent are they used, in what combinations and for how long? This is the question that the EPICOR registry (long-term follow up of antithrombotic management Patterns In acute CORonary syndrome patients, NCT01171404) (8) has attempted to answer with its multiple analyses and results. (9-11). EPICOR is a prospective, observational, multicenter, international registry (involving 20 countries in Europe and Latin America) of patients surviving hospitalization for ACS followed-up for 2 years, with a twin registry, EPICOR Asia, (9) which essentially collected the same information. Up to now, this registry has been useful to study antithrombotic therapy patterns of use (10, 11) and regional differences in clinical management, (12, 13) to calculate use of resources and costs, (14) to develop risk scales, (15-17) or to analyze specific groups of patients. (18)

In this issue of the Argentine Journal of Cardiology, Marcelo Trivi et al. publish an article on the follow-up results of the EPICOR cohort in Argentina. (19) The main findings of this study are: 1) A surprisingly elevated percentage of Argentine patients with ACS persisted with double antiplatelet therapy beyond two years after discharge; 2) global mortality at two years was 4.8% for ST-segment elevation ACS (STE-ACS) and 7.3% for non ST-segment elevation ACS (NSTEMI-ACS) and 3) there was a high incidence of other ischemic events (12.9% in STE-ACS and 16.7% in NSTEMI-ACS) with few relevant hemorrhagic events (1.8%).

The high percentage of patients with mid- and long-term double antiplatelet therapy should be placed in context. Results of 80% of patients treated with double antiplatelet therapy at one year and 53% at two years are reported, with no difference between those with or without ST-segment elevation. This high incidence in 2010-2011 contrasts with the lack of evidence that existed at that time to support this decision, since both studies that would endorse this strategy, the Dual Antiplatelet Therapy (DAPT) and the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54), were published in 2014 (5) and 2015, (6) respectively. Even now, the indication of prolonged double antiplatelet treatment is restrictive, with IIb recommendation, level of evidence A, in the European Society of Cardiology clinical practice guidelines, (20) since its use for more than one year after the event should be sensibly counterbalanced with the individual patient hemorrhagic risk. It is possible that the more recent TIGRIS (long Term risk clinical management and healthcare Resource utilization of stable coronary artery disease in post-myocardial infarction patients) registry, (21) can provide a new perspective on the patterns of antithrombotic drug use in the stable ischemic patient.

The study global mortality can be compared with that observed in other regions also participating in the EPICOR study. However, Argentina reports 9% mortality at 2 years after discharge for STE-ACS, considerably higher than that found in Latin America (7.4%) which is in itself the EPICOR region with the greatest mortality (other examples: Northern Europe 2.5%, Southern Europe 4.1% and Eastern Europe 4.9%) (12). Even though the number of patients included is small to make generalizations, this is a worrying finding that requires specific analysis of its causes (mostly of coronary artery origin according to the article) and

REV ARGENT CARDIOL 2019;87:1-3. <http://dx.doi.org/10.7775/rac.v87.i1.14625>

SEE RELATED ARTICLE: Rev Argent Cardiol 2019;87:6-14. <http://dx.doi.org/10.7775/rac.v87.i1.14242>

Address for reprints: Héctor Bueno, MD, PhD. Centro Nacional de Investigaciones Cardiovasculares (CNIC). Melchor Fernández Almagro, 3 28029 Madrid (Spain). hbueno@cnic.es. Phone: (+34) 914 531 200 Ext: 4110. Fax: (+34) 914 531 265

¹ National Center for Cardiovascular Research (CNIC), Madrid, Spain

² CIBER of Cardiovascular Disease (CIBERCV), Madrid, Spain

³ Department of Cardiology, Hospital Universitario 12 de Octubre and Healthcare Research Institute, Hospital 12 de Octubre (imas12)

⁴ School of Medicine. Universidad Complutense, Madrid, Spain

the search of possible solutions. Argentina reports 6.2% mortality for NSTEMI-ACS, lower than that found in Latin America (9.7%) and some European regions (Eastern Europe: 7.6%; Southern Europe: 6.7%), but higher than that observed in Northern Europe (4.6%). (13) It is important to point out that, in Argentina, mortality after hospital discharge in STEMI-ACS patients was unusually higher than in those with NSTEMI-ACS, despite in-hospital mortality, normally higher in STEMI-ACS patients than after hospital discharge, (22) was not considered in the study design.

Finally, even though cardiovascular events are not clearly. Also, defined in the manuscript of Trivi et al., it is necessary to point out that the 12.9% and 16.9% rate of events in patients with STEMI-ACS and NSTEMI-ACS, respectively, stress the magnitude of the improvement opportunity we face. It is necessary to enhance all the secondary cardiovascular prevention strategies, from lifestyle changes (diet, physical activity and smoking cessation) to pharmacotherapy, including prescription and adherence to medications with proven efficacy, to improve the prognosis of patients with ACS. (7, 23)

It is important to emphasize the limitations of observational studies: problems of representativeness, inclusion and follow-up biases, inability to infer causal relationships, etc.... They are real. However, it is impossible to transform reality if this is unknown. Lacking clear mirrors of reality, as the Swedish or Danish models of systematic, obligatory national hospital registries, linked to prescription and survival information sources, it is better -despite its limitations- to have a distorted and blurred reflection of voluntary registries, than no information at all. Therefore, we cannot yet go without observational studies, as they often are the only source of analysis of healthcare quality and the lever to improve it in real life. In this sense, the information of EPICOR Argentina is welcome if it provides changes to improve the care and prognosis of patients during and after suffering an ACS.

Conflicts of interest

The EPICOR study is financed by AstraZeneca and Dr. Bueno is scientific coordinator of this study. He receives financial support from Instituto de Salud Carlos III (PIE16/00021, PI17/01799) and from AstraZeneca, BMS, Janssen and Novartis for research projects and has received payment for advice, conferences or as support for congress assistance from AstraZeneca, Bayer, BMS-Pfizer, Ferrer, MEDSCAPE-the heart.org, Novartis and Servier..

REFERENCES

1. Antithrombotic_Trialists'_Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86. <http://doi.org/ckrg7m>
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Eleva-

- tion. *N Engl J Med* 2001;345:494-502. <http://doi.org/d8ffxs>
3. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al, TRITON-TIMI 38 Investigators. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2007;357:2001-15. <http://doi.org/d2spwt>
4. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al, PLATO Investigators, Freij A, Thorsén M. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009;361:1045-57. <http://doi.org/cw5mfq>
5. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. *N Engl J Med* 2014;371:2155-66. <http://doi.org/f6sh79>
6. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *N Engl J Med* 2015;372:1791-800. <http://doi.org/6md>
7. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs. *J Am Coll Cardiol* 2015;66:1273-85. <http://doi.org/f3hx2x>
8. Bueno H, Danchin N, Tafalla M, Bernaud C, Annemans L, Werf F Van de. EPICOR (long-term follow-up of antithrombotic management Patterns in acute CORonary syndrome patients) study: rationale, design, and baseline characteristics. *Am Heart J* 2013;165:8-14. <http://doi.org/cv72>
9. Huo Y, Lee SW-L, Sawhney JPS, Kim H-S, Krittayaphong R, Nhan VT, et al. Rationale, Design, and Baseline Characteristics of the EPICOR Asia Study (Long-term follow-up of antithrombotic management patterns in Acute CORonary Syndrome patients in Asia). *Clin Cardiol* 2015;38:511-9. <http://doi.org/f8wfdt>
10. Bueno H, Sinnaeve P, Annemans L, Danchin N, Licour M, Medina J, et al; EPICOR Investigators. Opportunities for improvement in anti-thrombotic therapy and other strategies for the management of acute coronary syndromes: Insights from EPICOR, an international study of current practice patterns. *Eur Heart J Acute Cardiovasc Care* 2016;5:3-12. <http://doi.org/czhc>
11. Bueno H, Pocock S, Danchin N, Annemans L, Gregson J, Medina J, et al. International patterns of dual antiplatelet therapy duration after acute coronary syndromes. *Heart* 2017;103:132-8. <http://doi.org/f9kmvr>
12. Rossello X, Huo Y, Pocock S, Werf F Van de, Chin CT, Danchin N, et al. Global geographical variations in ST-segment elevation myocardial infarction management and post-discharge mortality. *Int J Cardiol* 2017;245:27-34. <http://doi.org/gbxx4j>
13. Bueno H, Rossello X, Pocock S, Werf F Van de, Chin CT, Danchin N, et al. Regional variations in hospital management and post-discharge mortality in patients with non-ST-segment elevation acute coronary syndrome. *Clin Res Cardiol* 2018;107:836-44. <http://doi.org/gd4xkx>
14. Annemans L, Danchin N, Van de Werf F, Pocock S, Licour M, Medina J, et al. Pre- and in-hospital use of healthcare resources in patients surviving acute coronary syndromes. An analysis of the EPICOR registry. *Open Heart* 2016;3:e000347. <http://doi.org/czhd>
15. Pocock S, Bueno H, Licour M, Medina J, Zhang L, Annemans L, et al. Predictors of one-year mortality at hospital discharge after acute coronary syndromes: A new risk score from the EPICOR (long-term follow up of antithrombotic management patterns in acute CORonary syndrome patients) study. *Eur Heart J Acute Cardiovasc Care* 2015;4:509-17. <http://doi.org/czhf>
16. Pocock SJ, Huo Y, Werf F Van de, Newsome S, Chin CT, Vega AM, et al. Predicting two-year mortality from discharge after acute coronary syndrome: An internationally-based risk score. *Eur Heart J Acute Cardiovasc Care* 2017;2048872617171963. <http://doi.org/gbqw92>
17. Rossello X, Bueno H, Pocock SJ, Werf F Van de, Danchin N, Annemans L, et al. Predictors of all-cause mortality and ischemic events within and beyond 1 year after an acute coronary syndrome: Results from the EPICOR registry. *Clin Cardiol* 2018;41:23116. <http://doi.org/gfnmfv>
18. Stepinska J, Wojtkowska I, Annemans L, Danchin N, Pocock SJ, de Werf FV, et al. Long-Term Outcome of Acute Coronary Syndromes in Patients on Chronic Oral Anticoagulants: Data from the EPICOR Study. *Curr Vasc Pharmacol* 2018 Dec 27. doi: 10.2174/157016111766618127122355. PMID: 30588886 <http://doi.org/czgh>
19. Trivi M, Lakowsky A, Zeballos C, Duronto E, Lobo Márquez L, Rapallo C, et al. EPICOR: registro prospectivo de tratamiento antitrombótico en síndromes coronarios agudos. *Rev Argent Cardiol*

2019;87:6-14.

20. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al, ESC Scientific Document Group L, ESC Committee for Practice Guidelines (CPG) P, ESC National Cardiac Societies S, Andreotti F, Antman E, Barbato E, Bassand J-P, Bugiardini R, Cikirikcioglu M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60. <http://doi.org/gcps5k>

21. Westermann D, Goodman SG, Nicolau JC, Requena G, Maguire A, Chen JY, et al; TIGRIS Study Investigators. Rationale and design

of the long-Term risk, clinical management, and healthcare Resource utilization of stable coronary artery disease in post-myocardial infarction patients (TIGRIS) study. *Clin Cardiol* 2017;40:1197-204. <http://doi.org/gcpmc6>

22. Pedersen F, Butrymovich V, Kelbæk H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014;64:2101-8. <http://doi.org/f2v72t>

23. Setoguchi S, Glynn RJ, Avorn J, Mittleman MA, Levin R, Winkel-mayer WC. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008;51:1247-54. <http://doi.org/c77r9b>