Rev Esp Cardiol. 2022;75(8):623–625

Image in cardiology

Drug-eluting stents and contemporary dual antiplatelet therapy in revascularized STEMI. The times they are a-changin'?

Stent farmacoactivo y régimen contemporáneo de doble antiagregación plaquetaria en el IAMCEST revascularizado. ¿Los tiempos están cambiando?

Luis M. Rincón,[a,b] Eduardo Villacorta,[a,b] and Pedro L. Sánchez[a,b,*]

[a] *Servicio de Cardiología, Hospital Universitario de Salamanca-IBSAL, Universidad de Salamanca, Salamanca, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

The prognosis of ST-segment elevation acute myocardial infarction (STEMI) has improved significantly in the last 2 decades.[1] While mechanical dilatation of the coronary arteries and dual antiplatelet therapy were considered to be the main drivers of success in randomized clinical trials evaluating their efficacy,[2,3] the effectiveness of regional care networks (the infarction code) and the incorporation of the recommendations established in clinical practice guidelines are beginning to be evaluated in cohorts of patients with STEMI and prolonged follow-up.[4,5]

Mechanical dilatation of the culprit artery of STEMI via primary angioplasty is the reperfusion strategy preferentially recommended by current clinical practice guidelines.[2] The first randomized clinical trial to compare primary angioplasty vs fibrinolysis and its benefit on long-term mortality dates back to 1999; with a total of 395 patients, the trial revealed a 46% relative reduction in mortality[6]; these results have been corroborated in numerous subsequent randomized clinical trials.[7] Coronary stent implantation during primary angioplasty is associated with a lower incidence of reinfarction and coronary revascularization; however, no type of stent—whether conventional or drug-eluting—has demonstrated mortality reductions in the numerous randomized clinical trials conducted since about 2000.[8,9] The clinical practice guidelines[2] preferentially recommend drug-eluting stents over bare-metal stents with a class I recommendation with level of evidence A due to their lower rates of restenosis and need for future revascularization.

It is worth remembering that the indication for dual antiplatelet therapy in STEMI patients revascularized with primary angioplasty is not based on any clinical trial in this context. The initial effectiveness of dual antiplatelet therapy with clopidogrel plus aspirin is based on the results of clinical trials with planned angioplasty conducted in the first few years of the century.[10,11] Subsequently, the TRITON TIMI 38 study of prasugrel (2007) and the PLATO study of ticagrelor (2009) revealed the benefits of both drugs vs clopidogrel in patients with acute coronary syndrome and in the context of dual antiplatelet therapy.[12,13] However, an analysis of the benefit of prasugrel in the TRITON TIMI 38 study that was limited to the 2438 patients with STEMI treated with primary angioplasty failed to show a reduced incidence of the primary composite endpoint of the study: cardiovascular death, reinfarction, or stroke at 15 months of follow-up (11.6% with clopidogrel vs 10.2% with prasugrel; hazard ratio [HR] = 0.87; 95% confidence interval [95%CI], 0.68-1.11; P = .26).[14] Similarly, an analysis of the PLATO study specifically in the 7544 patients with STEMI treated with primary angioplasty also failed to identify significant results in the same composite endpoint at 12 months (10.8% with clopidogrel vs 9.4% with ticagrelor; HR = 0.87; 95%CI, 0.75-1.01; P = .07).[15] Based on the TRITON TIMI 38 and PLATO randomized clinical trials of prasugrel and ticagrelor, the clinical practice guidelines assign a class I recommendation with level of evidence A[2] to dual antiplatelet therapy in STEMI patients treated with primary angioplasty and gives preference to the prescription of both vs clopidogrel.

Prolongation of dual antiplatelet therapy involving the combination of aspirin with a $P2Y_{12}$ inhibitor (prasugrel, ticagrelor, or clopidogrel) until 12 months is recommended in patients with STEMI revascularized with primary angioplasty. This timeframe is set by the length of treatment established for the performance of primary clinical trials with clopidogrel, prasugrel, and ticagrelor,[10,12,13] but not by any specific study of this topic. Similarly, the clinical practice guidelines allow prolongation of the dual antiplatelet therapy to at least 12 months in STEMI patients treated with primary angioplasty, with a class I recommendation with level of evidence A.[2]

In a recent article published in *Revista Española de Cardiología*, Ribera et al.[16] thoroughly analyze whether the adoption of the practices recommended in the guidelines improved the prognosis of 14 841 patients with STEMI in the Catalan *Codi IAM* registry and enrolled between 2010 and 2017.[16] In a laudable effort to analyze in real-life clinical practice the impact of drug-eluting stents and a more contemporary, potent, and prolonged dual antiplatelet therapy, the authors studied the occurrence of adverse cardiovascular events, death, and bleeding at 2-year intervals. The results challenge the foundations of our routine practice and leave us wondering if we have reached our limit, if we should question the evidence supporting the guidelines, and, fundamentally, how we should incorporate the results.

An initial reading illustrates that the progressive adoption of the treatments recommended in the guidelines have not clearly decreased the rates of major adverse cardiovascular events, which

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2021.10.011

* Corresponding author: Servicio de Cardiología, Hospital Universitario de Salamanca, P.º de San Vicente 58, 37007 Salamanca, Spain.
E-mail address: pedrolsanchez@secardiologia.es (P.L. Sánchez).

Available online 9 May 2022

https://doi.org/10.1016/j.rec.2022.02.013

forces us to "pay attention to the small print". Two-year overall mortality in patients who survived an STEMI increased from 5.9% in 2010 to 2011 to 6.2% in 2016 to 2017, despite the progressive and predominant incorporation of drug-eluting stents, the prescription of potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor), and the prolongation of the dual antiplatelet therapy time, which increased from 2 to 10 months. The analysis adjusted by age, sex, kidney function, previous infarction, diabetes, heart failure in Killip class III/IV, and anterior infarction enabled identification of a statistically significant and clinically disappointing decrease in the main composite endpoint (death, infarction, stroke, or new revascularization; odds ratio = 0.995; 95%CI, 0.99-0.999), largely due to a reduction in new revascularizations.

Based on our interpretation, these real-life outcomes exactly reproduce the outcomes of the related randomized clinical trials. Accordingly, the researchers observed a reduction in the rate of new revascularizations that was possibly attributable to the increase in drug-eluting stent implants in primary angioplasty, analogously to the randomized clinical trials performed in this context.[8,9] The authors did not identify a decreased incidence of death, infarction, or stroke, as also seen in the analysis of the patients with STEMI treated with primary angioplasty in the TRITON TIMI 38 and PLATO trials.[14,15] Finally, the absence of randomized clinical trials evaluating the optimal prolongation time for dual antiplatelet therapy in STEMI patients revascularized with primary angioplasty highlights even further the relevance of the data from this study, with prolongation of the dual antiplatelet therapy seeming to have no significant effect on the prognosis of patients with STEMI revascularized with primary angioplasty in the context of a regional care network such as the *Codi IAM* in Catalonia. It is true that adherence to the guideline recommendations is incomplete, which would limit the prognostic benefit of the interventions studied, and that the comparison of timeframes does not include the potential benefit of other variables not specifically studied and whose summed effect should not be underestimated (eg, the use of more potent lipid-lowering therapies or the spread of cardiac rehabilitation units).

We must praise this type of study, which integrates data from a regional infarction code network with those obtained from the use of health care resources and drugs, under the principle "what is not evaluated loses value". The exhaustive character of the registry, which includes almost all STEMI patients in the area of reference, in conjunction with an elegant statistical analysis, serves as a paradigm for other possible research initiatives in the real-life setting in this field. At the same time, these data will inevitably be compared with those from larger national registries. We would like to highlight 2 related examples: one from northern Europe, specifically, the Swedish SWEDEHEART registry[4]; the latest analysis of temporal trends in STEMI from 1995 to 2014 identified gradual improvements in survival and the risk of adverse ischemic events, which the authors linked to the progressive implementation of evidence-based treatments.[4] However, careful reading reveals that the main determinant of prognosis is urgent revascularization because, after the universalization of the primary angioplasty strategies after 2008, the survival curves in the following years practically overlap. The other study, that performed by Cequier et al.,[5] examined the association between the implementation of the infarction code in Spanish autonomous communities and in-hospital mortality by analyzing hospital discharge data from the Spanish National Health System between 2003 and 2012. Implementation of the regional infarction code was associated with a 14% reduction in the risk-standardized mortality rate. Nonetheless, their study also provided valuable data on the reduction in STEMI mortality in autonomous communities where, in those years, the infarction code program had not yet begun. This observation is key to understanding the existence of an individual benefit of a specific treatment in STEMI and that it is possibly more difficult to recognize this benefit since the widespread use of coronary reperfusion treatments.

Finally, physicians depend more and more on clinical practice guidelines in their daily practice. These guidelines synthesize large amounts of information, help us to make clinical decisions, and protect us from malpractice lawsuits. However, the evidence for determining the type of recommendation is not always powerful and the generalization of these recommendations should be examined in real-life studies, such as that discussed here. The guidelines of the European Society of Cardiology reflect this limitation and include the recommendation to create registries of unselected clinical data as areas for future research.[2] It remains to be seen whether the publication of the outcomes of clinical practice translates into the drafting of treatment recommendations and the performance of randomized clinical trials. In this regard, the residual risk of new adverse cardiovascular events in patients who have had a STEMI is considerably lower in 2022 than in previous decades. It is undoubtedly difficult for a single intervention to show additional prognostic benefits. However, the lack of solid benefits derived from the application of a set of combined interventions (drug-eluting stents and prolonged and potent dual antiplatelet therapy) should make us ask if a "one size fits all" strategy can still be applicable in the future to all patients with STEMI. We believe that the elevated economic impact of the new treatments already available in the cardiovascular field (PCSK9 inhibitors, SGLT2 inhibitors, valsartan/sacubitril, direct oral anticoagulants, and many more) in European health care systems mean that the clinical practice guidelines should reconsider how the new evidence should be incorporated to guarantee its sustainability; a priority is to identify patients with a higher risk of new events and to introduce the concept of cost-effectiveness in the recommendations. Until then, and after the study by Ribera et al.,[16] the guidelines should reflect the inability of drug-eluting stent implantation in STEMI patients revascularized with primary angioplasty or the selection of contemporary prolonged dual antiplatelet therapy regimens (prasugrel and ticagrelor) to reduce the incidence of death, infarction, or stroke in this clinical context vs the implantation of bare-metal stents and the administration of dual antiplatelet therapy with clopidogrel. In today's world, the optimization of health care resources is an obligation.

FUNDING

The Cardiology Department of University Hospital of Salamanca is a Research Center belonging to CIBERCV, Health Institute Carlos III (ISCIII), from which it receives funding to promote cardiovascular research.

CONFLICTS OF INTEREST

There are no conflicts of interests to declare.

REFERENCES

1. Pascual I, Avanzas P, Almendárez M, et al. IAMCEST, angioplastia primaria y recuperación de la esperanza de vida: ideas procedentes del estudio SurviSTEMI. *Rev Esp Cardiol.* 2021;74:829–837.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119–177.

3. Alfonso F, Sionis A, Bueno H, et al. Comments on the 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Rev Esp Cardiol.* 2017;70:1039–1045.
4. Szummer K, Wallentin L, Lindhagen L, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20?years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J.* 2017;38:3056–3065.
5. Cequier Áaue, Ariza-Solé A, Elola FJ, et al. Impact on mortality of different network systems in the treatment of ST-segment elevation acute myocardial infarction The Spanish Experience. *Rev Esp Cardiol.* 2017;70:155–161.
6. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1999;341:1413–1419.
7. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13–20.
8. Nordmann AJ, Hengstler P, Harr T, Young J, Bucher HC. Clinical outcomes of primary stenting versus balloon angioplasty in patients with myocardial infarction: a meta-analysis of randomized controlled trials. *Am J Med.* 2004;116:253–262.
9. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J.* 2007;28:2706–2713.
10. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527–533.
11. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA.* 2005;294:1224–1232.
12. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001–2015.
13. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057.
14. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet.* 2009;373:723–731.
15. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation.* 2010;122:2131–2141.
16. Ribera A, Marsal JR, Faixedas MT, et al. Revascularized ST-segment elevation myocardial infarction Temporal trends in contemporary therapies and impact on outcomes. *Rev Esp Cardiol.* 2022. http://dx.doi.org/10.1016/j.rec.2021.10.011.