NEJM & The Lancet: CNIC-led REBOOT clinical trial challenges 40-year-old standard of care for heart attack patients

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REBOOT trial, coordinated by the CNIC, shows that treatment with beta-blockers provides no benefit to patients who experience an uncomplicated heart attack that leaves the contractile function of the heart intact.

An international clinical trial coordinated by the Centro Nacional de Investigaciones Cardiovasculares (CNIC), in collaboration with the Mario Negri Institute for Pharmacological Research in Milan, has found that beta-blockers—drugs commonly prescribed for a range of cardiac conditions—offer no clinical benefit for patients who have had an uncomplicated myocardial infarction (i.e., without deterioration of the heart function after the event).

The findings—published in two articles in *The New England Journal of Medicine* and *The Lancet* and presented today during a "**Hot Line**" session at the European Society of Cardiology (ESC) Congress in Madrid—overturn a treatment paradigm that has shaped clinical practice for more than four decades.

The REBOOT trial (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction) enrolled 8,505 patients with a left ventricular ejection fraction above 40% after a heart attack, across 109 hospitals in Spain and Italy. Participants were randomly assigned to receive or not receive beta-blockers after hospital discharge. All patients received current standard of care and were followed for a median of nearly four years. The results showed no significant differences between the two groups in rates of death, recurrent heart attack, or hospitalization for heart failure.

Although generally considered safe, beta-blockers can cause side effects such as fatigue, bradycardia (low heart rate), and sexual dysfunction.

"REBOOT will change clinical practice worldwide," says principal investigator Dr. Borja Ibáñez, CNIC Scientific Director, cardiologist at *Hospital Universitario Fundación Jiménez Díaz*, and a group leader in the Spanish cardiovascular research network CIBERCV. "Currently, more than 80% of patients with uncomplicated myocardial infarction are discharged on beta-blockers. The REBOOT findings represent one of the most significant advances in heart attack treatment in decades."

After a heart attack, cardiac contractile function can be overtly deteriorated (left ventricular ejection fraction below 40%), moderately reduced (40-50%), or preserved (above 50%). The vast majority patients these days (approx. 70%) survive the heart attach with a preserved cardiac function, a smaller proportion (approx. 20%) with a moderately reduced function, and 10% with overtly reduced cardiac function. REBOOT enrolled patients from the 2 former groups since there was no evidence of the benefits of beta-blockers on these types of patients. While the trial results showed no benefit of beta-blockers for the study population overall, the treatment did appear to benefit the patient subgroup with moderately reduced contractile function. However, this subgroup constituted a relatively small proportion of the study population, and the small sample size prevented the team from drawing firm conclusions on this subgroup.

To address this question in this specific subgroup of patients, the researchers carried out a joint meta-analysis with other smaller trials that also included patients with these characteristics. The meta-analysis, published in *The Lancet*, confirms that beta-blockers significantly reduce the risk of death, recurrent heart attack, or heart failure only in post-infarction patients with moderately reduced cardiac contractile function.

Dr. Xavier Rosselló—CNIC scientist, cardiologist at University Hospital Son Espases in Mallorca, and one of the REBOOT study leaders—explains: "Taken together, these two studies provide compelling evidence that post-infarction patients with fully preserved contractile function (ejection fraction above 50%) do not benefit from beta-blockers, whereas those with moderate or greater dysfunction (ejection fraction below 50%) do."

Dr. Borja Ibáñez, who led the meta-analysis, adds: "These findings will form the basis for future treatment of myocardial infarction and will drive a major shift in clinical practice guidelines."

Every year, more than 2 million people in Europe suffer a heart attack, including around 70,000 in Spain. Until now, the majority were discharged on beta-blockers—a practice now called into question.

“After a heart attack, patients are typically prescribed multiple medications, which can make adherence difficult,” explains Dr. Ibáñez. “Beta-blockers were added to standard treatment early on because they significantly reduced mortality at the time. Their benefits were linked to reduced cardiac oxygen demand and arrhythmia prevention. But therapies have evolved. Today, occluded coronary arteries are systematically reopened rapidly, drastically lowering the risk of serious complications such as arrhythmias. In this new context—where the extent of heart damage is smaller—the need for beta-blockers is unclear. While we often test new drugs, it's much less common to rigorously question the continued need for older treatments.”
That was the motivation behind REBOOT-CNIC. “The trial was designed to optimize heart attack care based on solid scientific evidence and without commercial bias,” said Dr. Ibáñez. “These results will help simplify and streamline treatment, reduce adverse effects, and improve the quality of life for thousands of patients every year.”
Importantly, REBOOT was conducted without pharmaceutical industry funding.

A landmark in European cardiovascular research

More than 500 researchers from across Spain and Italy participated in REBOOT on a voluntary basis. A total of 109 hospitals—74 in Spain and 35 in Italy—recruited 8,505 patients. The Italian arm was coordinated by the Mario Negri Institute in Milan under the leadership of cardiologist Roberto Latini, through a collaboration agreement with the CNIC.

As Dr. Rosselló explains: “The credit for carrying out the largest clinical trial ever conducted on this question belongs not only to CNIC, but above all to the more than 100 participating hospitals and their teams, who worked tirelessly for six years with the sole aim of improving care for heart attack patients worldwide.”

Through its Clinical Trials Coordination Unit (CTCU), the CNIC led the logistics and management of the trial, showcasing the Spanish research system’s capacity to deliver clinical studies with global impact. The CTCU has become a key hub for coordinating large-scale cardiology trials with a purely scientific mission.

The success of REBOOT also relied on the collaboration between the CNIC, the Spanish Society of Cardiology (SEC), and CIBERCV. According to SEC president Dr. Luis Rodríguez Padial, “REBOOT not only changes heart attack treatment—it also changes how clinical trials are designed and run in Spain.”

Underlining this point, Dr. Ibáñez emphasizes that the joint leadership by CNIC, SEC, and CIBERCV “reflects Spain’s enormous potential when a transformative project is combined with strong scientific leadership.”

Dr. Valentín Fuster, CNIC General Director, President of Mount Sinai Fuster Heart Hospital , and one of the senior investigators on REBOOT, notes: “This trial will reshape all international clinical guidelines. It joins other landmark trials led by CNIC—such as SECURE with the polypill and DapaTAVI, which links SGLT2 inhibition to TAVI—that have already transformed the global approach to cardiovascular disease.”

The trial was funded by the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) an affiliate center of the Carlos III Health Institute (ISCIII), an executive agency of the Spanish Ministry of Science, Innovation and Universities. The clinical trial was carried out with the collaboration of the Spanish Society of Cardiology (SEC), and CIBERCV.

- *Rosselló, X., Prescott, E., Kristensen, A. M., Ibanez, B., et al. (2025). Beta-blockers after myocardial infarction in patients without heart failure. The New England Journal of Medicine. Advance online publication. https://doi.org/10.1056/NEJMoa2505985*

- Rosselló, X., Prescott, E., Kristensen, A. M., Ibanez, B., et al. (2025). Beta-blockers after myocardial infarction with mildly reduced ejection fraction: An individual patient data meta-analysis of randomised controlled trials. The Lancet. Advance online publication. https://doi.org/10.1016/S0140-6736(25)01592-2

Hospitals and centers participating in the REBOOT trial

1. Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, España
2. Departamento de Cardiología, Hospital Universitario Fundación Jiménez Díaz e Instituto de Investigación Sanitaria-Fundación Jiménez Díaz (IIS-FJD, UAM), Madrid, España
3. Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares (CIBERCV), España
4. Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milán, Italia
5. Departamento de Cardiología, Hospital Universitario Son Espases, Instituto de Investigación Sanitaria Islas Baleares y Universitat de les Illes Balears (UIB), Palma de Mallorca, España
6. Departamento de Medicina Interna, Universidad de La Laguna, y Departamento de Cardiología, Hospital Universitario de Canarias; Instituto de Investigación Sanitaria de Canarias, Tenerife, España
7. Hospital Universitario de León, España
8. Departamento de Cardiología, Ospedale Guglielmo da Saliceto, Piacenza, Italia
9. Departamento de Cardiología, Hospital Universitario de Salamanca, Instituto de Investigación Biomédica de Salamanca (IBSAL), España
10. Departamento de Cardiología, Hospital Universitario Reina Sofía, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Universidad de Córdoba, España
11. Departamento de Cardiología, Hospital Universitari Vall d'Hebron, Barcelona, España
12. Departamento de Cardiología, Hospital Universitario Álvaro Cunqueiro, Vigo, España
13. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, Londres, Reino Unido
14. Grupo Jóvenes Cardiólogos, Sociedad Española de Cardiología (SEC), Madrid, España
15. Hospital de Burgos, España
16. Servicio de Cardiología, Complexo Hospitalario Universitario de A Coruña (CHUAC), Instituto de Investigación Biomédica de A Coruña (INIBIC), A Coruña, España
17. Departamento de Cardiología, Hospital Ruber Juan Bravo Quirónsalud y Facultad de Medicina, Salud y Deporte, Universidad Europea, Madrid, España
18. Cardiology Division, San Luigi Gonzaga University Hospital, Orbassano, Turín, Italia
19. Hospital Marqués de Valdecilla, IDIVAL, Santander, España
20. Departamento de Cardiología, Ospedale S. Anna e S. Sebastiano, Caserta, Italia
21. Hospital Universitario Virgen del Rocío, Sevilla, España
22. Hospital Universitario San Cecilio, Granada, España
23. Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (i+12), Universidad Complutense de Madrid, España
24. Hospital de Jaén, España
25. Dipartimento di Cardiologia, Ospedale Bolognini, Seriate, Italia
26. Hospital San Juan de la Cruz, Úbeda, España
27. Hospital Virgen de los Lirios, Alcoy, España
28. Departamento de Cardiología, Complejo Hospitalario Universitario de Santiago de Compostela, IDIS, España
29. Hospital San Agustín de Avilés, España
30. Hospital Lucus Augusti, Lugo, España
31. Departamento de Cardiología, Hospital Clínic Barcelona; Institut d'Investigació August Pi i Sunyer (IDIBAPS); Universitat de Barcelona, España
32. Departamento de Cardiología, Hospital Universitario de Torrejón, Universidad Francisco de Vitoria, Madrid, España
33. Hospital Joan XXIII, Tarragona, España
34. Hospital Universitario Virgen de la Macarena, Sevilla, España

35. Departamento de Cardiología, Hospital Virgen de la Arrixaca, IMIB-Arrixaca y Universidad de Murcia, España
36. Hospital Arnau de Vilanova, Lleida, España
37. Hospital Clínico Universitario de Valladolid, España
38. Departamento Cardiovascular, Misericordia Hospital, Grosseto, Italia
39. Departamento de Cardiología, Hospital Universitari i Politècnic La Fe, Valencia, España
40. University Hospital La Luz, Madrid, España
41. Ospedale San Filippo Neri, Italia
42. Hospital Universitario Miguel Servet, Zaragoza, España
43. Hospital de Navarra, España
44. Hospital San Juan, Alicante, España
45. Hospital Clínico San Carlos, IdISSC, Universidad Complutense, Madrid, España
46. Ospedale San Paolo, Bari, Italia
47. Hospital Montecelo, Pontevedra, España
48. Ospedale Civile di Legnano, Italia
49. Hospital Maggiore di Bologna, Italia
50. Ospedale di Udine, Italia
51. Ospedale Gualdo Tadino, Gubbio, Italia
52. U.O.C. Cardiologia Ospedaliera, PO ASMN, Azienda USL di Reggio Emilia - IRCCS, Italia
53. Departamento de Cardiología, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, y Facultad de Medicina, Universidad Complutense de Madrid, España
54. Ospedale di Vaio, Fidenza, Italia
55. Departamento de Cardiología e ICCU, AOU delle Marche, Ancona, Italia
56. Hospital Universitario Fundación Alcorcón, Madrid, España
57. Unidad Cardiovascular, Ospedale Infermi, Rimini, Italia
58. Mount Sinai Fuster Heart Hospital, Nueva York, NY, EE. UU.