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4 **Rationale and design of the pragmatic clinical trial *tREatment with Beta-***  
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7 ***blockers after myOcardial infarction withOut reduced ejection fracTion***  
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10 **(REBOOT)**  
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4 **Abstract**  
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6 **Background.** There is a lack of evidence regarding the benefits of  $\beta$ -blocker treatment after  
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invasively managed acute myocardial infarction (MI) without reduced left ventricular ejection fraction (LVEF).

**Methods and Results.** Treatment with Beta-blockers after myocardial infarction without reduced ejection fraction (REBOOT) trial is a pragmatic, controlled, prospective, randomized, open-label blinded endpoint (PROBE design) clinical trial testing the benefits of  $\beta$ -blocker maintenance therapy in patients discharged after MI with or without ST-segment elevation. Patients eligible for participation are those managed invasively during index hospitalization (coronary angiography), with LVEF >40%, and no history of heart failure (HF). At discharge, patients will be randomized 1:1 to  $\beta$ -blocker therapy (agent and dose according to treating physician) or no  $\beta$ -blocker therapy. The primary endpoint is a composite of all-cause death, nonfatal reinfarction, or HF hospitalization over a median follow-up period of 2.75 years (minimum 2 years, maximum 3 years). Key secondary endpoints include the incidence of the individual components of the primary composite endpoint, the incidence of cardiac death, and incidence of malignant ventricular arrhythmias or resuscitated cardiac arrest. The primary endpoint will be analyzed according to the intention-to-treat principle.

**Conclusion.** The REBOOT trial will provide robust evidence to guide the prescription of  $\beta$ -blockers to patients discharged after MI without reduced LVEF.

**Keywords**

$\beta$ -blockers; acute myocardial infarction; left ventricular ejection fraction; randomized clinical trial.

## Introduction

The clinical benefit of  $\beta$ -blockers after a myocardial infarction (MI) in patients with reduced left ventricular ejection fraction (LVEF) is supported by solid evidence from modern trials.<sup>1-3</sup> However, the evidence for prescribing  $\beta$ -blockers after an uncomplicated MI in patients with LVEF >40% is less well established.<sup>4</sup> With the exception of the CAPRICORN trial,<sup>5</sup> which only recruited patients with LVEF  $\leq$ 40%, all randomized clinical trials testing the benefits of post-MI  $\beta$ -blocker maintenance were performed in the pre-reperfusion era. Pooled data showed that post-MI  $\beta$ -blocker therapy reduced the risk of death by 23% (95%CI 15-31%) over a 2-year follow-up,<sup>1</sup> suggesting an annual reduction of 1.2 deaths and 0.9 reinfarctions per 100 patients. However, since these trials were performed, the clinical scenario has changed dramatically, and timely reperfusion is now the mainstay treatment for ST-segment elevation MI (STEMI). Compared with invasive management, reperfusion significantly improves myocardial healing after MI and leaves the myocardium less vulnerable to arrhythmia and heart failure (HF).<sup>6</sup> Systematic early angiography and revascularization has also massively reduced the incidence of adverse events after non-ST elevation MI (NSTEMI).<sup>7</sup> In addition to treating infarct-related arteries (IRA), current standard therapy includes complete revascularization for patients with multivessel disease. There has also been a significant improvement in pharmacotherapy, and, despite regional variations across countries,<sup>8</sup> most post-MI patients are prescribed potent antithrombotics, statins, and other agents that improve prognosis.<sup>9</sup> Another important consideration is that the definition of MI has changed hugely since the mid-1980s, and diagnosis by high sensitivity troponin now classifies patients with MI who previously would have been diagnosed with unstable angina.<sup>10</sup> Together, these diagnostic and therapeutic improvements have had a massive impact in the survival of post-MI patients.<sup>11</sup> Within this changing scenario, the clinical benefit of  $\beta$ -blockers after uncomplicated MI is a long-standing clinical question.<sup>12</sup>

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4 In the absence of prospective randomized trials, attempts to evaluate the clinical benefit of  $\beta$ -  
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6 blockers after MI in patients without reduced LVEF have shown conflicting results, and the  
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8 observational nature of the data prohibits conclusions about causality.<sup>3, 13-18</sup> Clinical practice  
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10 guidelines of both the American College of Cardiology (ACC) and the European Society of  
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12 Cardiology (ESC) strongly recommend  $\beta$ -blockers for post-AMI patients with LVEF  $\leq 40\%$  (class  
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14 IA).<sup>9, 19-21</sup> While recognizing gaps in evidence and the need for further research, both scientific  
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16 societies also generally advocate the use of  $\beta$ -blockers in patients with LVEF  $>40\%$ .<sup>9, 21</sup>  
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18 Consequently,  $\beta$ -blockers are today given to a high proportion of post-MI patients without reduced  
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20 LVEF, reaching  $>80\%$  of patients in some cases.<sup>22</sup>  
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25 The lack of prospective clinical trials in the reperfusion era examining the effect of  $\beta$ -blockers  
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27 in post-MI patients with LVEF  $> 40\%$ , together with the drop in mortality linked to the introduction  
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29 of evidence-based medications, calls for a definitive randomized clinical trial addressing this highly  
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31 relevant clinical question.  
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## Methods

### Study design

The TREATment with Beta-blockers after myocardial infarction without reduced ejection fraction (REBOOT) trial (ClinicalTrials.gov Identifier: NCT03596385), is a pragmatic, controlled, prospective, randomized, open-label blinded endpoint (PROBE) superiority multi-center study conducted in Spain and Italy. The study flow chart is shown in **Figure 1**. Acute MI survivors who meet all inclusion criteria and none of the exclusion criteria are eligible for enrollment. Patients are recruited at or after hospital discharge, always within 14 days of the index event. Patients will be electronically 1:1 randomized to either the intervention group ( $\beta$ -blocker therapy, where the type and dose will be determined by the managing physician) or the control group (lack of  $\beta$ -blocker therapy). Patients will be treated according to current standards as judged by the attending physician. REBOOT will be performed in accordance with the ethical principles of the Declaration of Helsinki. The trial protocol has been registered at <http://register.clinicaltrials.gov> (NCT03596385) and the European Clinical Trials Database (EUDRACT 2017-002485-40). Patient data will be recorded in accordance with national personal data laws. The study protocol, including the patient information and informed consent form, has been approved by the relevant ethics committees in Spain (EC 79-17/FJD) and Italy (Reg.sperimentazioni n.2085, Prot.9144/2018; I.5/109).

### Study objectives and hypothesis

The primary endpoint is the effect of chronic  $\beta$ -blocker therapy on a composite measure of mortality and morbidity in post-MI patients with LVEF >40%. The hypothesis is that post-discharge  $\beta$ -blocker treatment will perform better than non-treatment for a composite of all-cause mortality, nonfatal reinfarction, or HF admission over a median follow-up period of 2.75 years.

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4 The secondary endpoints are the ability of  $\beta$ -blocker therapy to reduce the risk of i) each of  
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6 the primary endpoint measures separately (all-cause mortality, nonfatal reinfarction and HF  
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8 admission); ii) cardiac death; and iii) malignant ventricular arrhythmias (sustained ventricular  
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10 tachycardia, ventricular fibrillation, or resuscitated cardiac arrest).  
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### 16 Study population

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18 Candidates will be screened during index hospital admission of patients diagnosed with type  
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20 1 or type 2 MI.<sup>10</sup> Eligible patients with either STEMI or NSTEMI are invited to participate  
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22 immediately before hospital discharge; however, randomization can be after hospital discharge so  
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24 long as it takes place within 14 days of the index event. Patients are eligible as long as they have been  
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26 managed invasively during index admission (coronary angiography), regardless of the final  
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28 therapeutic approach (percutaneous coronary intervention [PCI], surgical revascularization, or  
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30 medical treatment) and regardless of the completeness of revascularization. Patients must have a pre-  
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32 discharge LVEF >40% by any imaging methodology. Previous  $\beta$ -blocker treatment, including the use  
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34 of  $\beta$ -blockers during the index hospitalization, is not an exclusion criterion. Patients are excluded if  
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36 they have a history of HF or Killip class  $\geq$  II at any time during the index episode or if they have an  
37  
38 absolute contraindication for  $\beta$ -blocker therapy. Further details on inclusion and exclusion criteria are  
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40 summarized in **Figure 2**.  
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### 49 Randomization and study intervention

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51 All patients must provide written informed consent prior to randomization. Afterwards,  
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53 patients will be centrally randomized via web or dedicated mobile app according to a permuted-block  
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55 design with random varying blocks of 4, 6, and 8 subjects, stratified by recruiting center. After  
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57 randomization, patients allocated to  $\beta$ -blocker therapy will receive the agent and dose chosen by their  
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59 treating physician. Given the pragmatic nature of the trial and that  $\beta$ -blocker therapy after MI is  
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4 current common practice, the study will not provide any medication to participants. The recruiting  
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6 centers are listed in the **Appendix**.  
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9 The only reason for patient withdrawal from the study is their desire to be excluded from the  
10 trial. The primary study endpoint will be assessed on an intention-to-treat (ITT) basis, and patients  
11 will therefore be assessed according to randomization, without regard for crossovers. Crossovers will  
12 remain in the trial, and follow-up will per protocol. However, the rate of and reasons for crossover  
13 will be recorded, and post-hoc analyses will consider only those patients adhering to the original  
14 randomization arm throughout follow-up.  
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### 26 Follow-up and study outcomes

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28 An overview of data collection during screening, enrollment, and treatment follow-up to  
29 study-end is shown in **Figure 3**. Follow-up monitoring will take place at three timepoints after  
30 enrollment (3±1, 15±3, 36±3 months) and will consist of phone calls, medical records review, and  
31 consultation of national registries, if needed. After identifying a potential event, the local investigator  
32 will collect and send the relevant information to the Clinical Trials Coordination Unit for blind  
33 adjudication by an independent committee. Follow-up will be for a minimum of 24 months and a  
34 maximum of 36 months (expected median follow-up is 2.75 years, assuming a constant inclusion  
35 rate). Two years after the last patient enrollment, all patients who have not reached the 36 months  
36 follow-up will be contacted for a final follow-up assessment.  
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49 The primary endpoint is the composite of all-cause death, nonfatal reinfarction, or HF  
50 hospitalization. Secondary endpoints will be i) individual primary endpoint components; ii) cardiac  
51 mortality; and iii) malignant arrhythmias (sustained ventricular tachycardia, ventricular fibrillation,  
52 or resuscitated cardiac arrest).  
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58 A sub-sample of  $\geq 1000$  consecutive patients will be invited to participate in the analysis of a  
59 tertiary endpoint assessing quality of life and functional class. Patients agreeing to participate in this  
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4 sub-study will be interviewed to determine their functional class (New York Heart Association and  
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6 Canadian Cardiovascular Society class) and to complete the European Quality of Life-5 Dimensions  
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8 (EQ-5D) questionnaire at 3 different timepoints: baseline (on enrollment) and at 3- and 15-month  
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10 follow-up. The primary, secondary, and tertiary endpoints are described in **Figure 4**.

### 11 12 13 14 15 16 Sample size calculation

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18 Assuming a 3-year incidence of the composite primary endpoint in the control arm of 10%  
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20 and a 5% patient withdrawal/loss to follow-up, and considering a randomization ratio of 1:1, a sample  
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22 size of 8468 participants (728 primary events) will provide a power of 85% to detect a relative risk  
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24 reduction of 20% in the  $\beta$ -blocker arm (hazard ratio, 0.80).

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27 To reduce the risk of underpowering due to an unexpectedly lower event rate, there will be a  
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29 blinded examination of the overall event rate a few months before the expected recruitment closing  
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31 date. If the data predict an overall primary event rate below 9% at end of follow-up, it will be assessed  
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33 the possibility of increasing the sample size to enhance statistical power.  
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### 39 Safety analysis and stopping rules

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41 Interim analyses will be performed on the primary and the secondary safety endpoints when  
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43 33% (240) and 66% (480) of events have been adjudicated. The interim analyses will follow the same  
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45 statistical plans as the final analysis. Stopping guidelines for efficacy analysis will be based on the  
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47 statistical Haybittle-Peto approach. Stopping guidelines for safety data are not predefined and will be  
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49 left to the discretion of the DSMB. The trial will not be stopped in case of futility, as this outcome  
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51 would be considered clinically relevant.  
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7 Statistical analysis  
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9           The null hypothesis is that the rate of the primary endpoint (composite of all-cause death,  
10 nonfatal reinfarction, or HF hospitalization over a minimum 2 years of follow-up) will be the same  
11 in the  $\beta$ -blocker arm and the control group. The alternative two-sided hypothesis is that the rate of the  
12 primary endpoint in the  $\beta$ -blocker group will be either greater or smaller than the rate in the control  
13 group. Cumulative incidence for each treatment group will be assessed and plotted with the Kaplan-  
14 Meier method, and will be compared using the log-rank test, followed by the multivariable Cox  
15 proportional hazards model. Treatment effect will be estimated with hazard ratios (HR) and  
16 corresponding 95% confidence intervals. Due to the randomization process and the large sample size  
17 in the trial, we do not expect major covariate imbalances between treatment groups. However, for  
18 exploratory purposes, standardized differences will be calculated, and known prognostic factors  
19 presenting an imbalance higher than 0.1 standardized difference will be included in the multivariable  
20 Cox model. For all tests, 2-sided p-values with an alpha  $\leq 0.05$  level of significance will be used.  
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36           Secondary endpoints will be assessed according to the same statistical analysis plan as the  
37 primary endpoints. The primary statistical analysis will be conducted according to the ITT principle.  
38 A per protocol (PP) secondary analysis will be performed (patient follow-up time truly on  $\beta$ -blockers  
39 or not).  
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47 Pre-specified subgroup analyses  
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49           A set of 12 pre-specified subgroup analyses will be undertaken using interaction models  
50 based on the primary analysis model. These analyses will include the subgroup factor and the  
51 treatment subgroup interaction factor as covariates. Estimates will be presented as hazard ratios for  
52 each subgroup alongside their p-value for interaction. Pre-specified subgroups are listed in **Figure 5**.  
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## Discussion

The REBOOT trial aims to fill the existing knowledge gap on the efficacy of post-MI  $\beta$ -blocker therapy in patients with LVEF > 40% and treated according to the state-of-the-art.<sup>12</sup> This randomized clinical trial will update the scientific evidence for the use of  $\beta$ -blockers as background therapy for one of the most prevalent chronic diseases worldwide.

In the pre-reperfusion era, more than 30 randomized trials compared oral maintenance  $\beta$ -blocker therapy vs. no  $\beta$ -blocker in post-MI patients. In the BHAT trial (3,837 post-AMI patients), propranolol consistently reduced relative risk across outcomes: 26% for all-cause death, 23% for cardiovascular death, and 23% for nonfatal acute MI over a 25-month follow-up.<sup>23</sup> In the Norwegian trial (1,884 post-MI patients), timolol showed a relative reduction of 39% for all-cause mortality and 28% for nonfatal MI over a follow-up period of 33 months.<sup>24</sup> These and other studies set the basis for the use of these drugs as state-of-the-art therapy for post-MI management. However, since those  $\beta$ -blocker trials were performed, the clinical scenario has changed considerably, with the introduction of better diagnostic tools (mainly high-sensitive troponins) and the widespread use of timely reperfusion for STEMI (mainly primary PCI), early invasive strategies for NSTEMI, and improved secondary preventive treatments.<sup>7, 12, 22</sup> There is therefore a need for a new scientific evaluation of the potential benefits and harms of  $\beta$ -blockers in the context of current clinical practice. The only available evidence in this context comes from observational studies and registries,<sup>3, 13-17</sup> which have major limitations.<sup>18</sup> A common feature of all these observational studies based on real life practice is the very high prescription rate for  $\beta$ -blockers (>80%). However, it is noteworthy that prescription of  $\beta$ -blockers has slightly decreased in recent years. In a recent Danish Nationwide registry,<sup>17</sup> the proportion of patients with a first MI that were discharge on  $\beta$ -blockers was 92% in 2003-2005, 88% in 2009-2011, and 67% in 2015-2018). Our study is carried out in Spain, where recent registry data identifies that the prescription of  $\beta$ -blockers after an acute MI is around 80%.<sup>25</sup> In any case, the very high proportion of  $\beta$ -blocker prescription implies a very high risk of bias. In particular, when the

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4 prescription of a therapy is non-random and is instead based on patients' clinical characteristics, this  
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6 creates the conditions for "confounding by indication", especially when these patient characteristics  
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8 are associated with the clinical outcome. Randomization is needed to ensure that individuals with  
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10 identical characteristics can be observed in both states, a condition lacking in all of these studies. The  
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12 only way to resolve the question of the benefits of post-MI  $\beta$ -blocker therapy is to conduct adequately  
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14 sized clinical trials.  
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18 REBOOT is a pragmatic trial very close to real life and thus have few exclusion criteria. Be  
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20 on  $\beta$ -blockers before or take them during index hospitalization do not disqualify for the trial. While  
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22 we anticipate that not many patients will be on maintenance  $\beta$ -blockers before enrollment, half of  
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24 these will be randomized to no  $\beta$ -blocker therapy. Withdrawal of maintenance  $\beta$ -blockers might have  
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26 an impact on events. In order to capture this potential effect, we set-up two actions: to establish the  
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28 first follow-up early (i.e. 3 months after enrollment) to collect data related to any potential  
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30 withdrawing consequences; and to pre-specify two subgroup analyses (see Figure 5), addressing this  
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32 issue: prior (before admission) vs no prior therapy with beta blockers; and in-hospital use vs lack of  
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34 in-hospital use of beta blockers.  
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39 To our knowledge, there are three ongoing clinical trials evaluating the effect of  $\beta$ -blockers  
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41 in patients discharged after MI without reduced LVEF: the BEtablocker Treatment After acute  
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43 Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction  
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45 (BETAMI) (NCT03646357); the Evaluation of Decreased Usage of Betablockers After Myocardial  
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47 Infarction in the SWEDEHEART Registry (REDUCE-SWEDEHEART) (NCT03278509); and the  
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49 Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection  
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51 Fraction (DANBLOCK) (NCT03778554).<sup>26</sup> The similarity of patient characteristics and some  
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53 endpoints across these trials offers the opportunity to address relevant secondary questions in future  
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55 individual-patient meta-analyses including close to 20,000 randomized patients. Researchers leading  
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57 these trials have already begun discussions in this regard.  
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4 The REBOOT trial design places special emphasis on conducting a pragmatic clinical trial,  
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6 for several reasons. First, post-MI  $\beta$ -blocker therapy is a low-cost intervention that forms part of  
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8 routine clinical practice in a postmarketing phase of drug evaluation. Another factor is that a large  
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10 sample size is needed to detect any potential treatment effect in a population with a declining  
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12 cardiovascular event rate due to the widespread use of evidence-based treatments.<sup>12</sup> Moreover, unlike  
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14 trials focused only on determining efficacy, which can overestimate benefits and underestimate harm,  
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16 a pragmatic approach mimics real-world practice and increases the external validity of the findings.  
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18 Our intervention is delivered as in normal practice, by regular staff using routinely available resources  
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20 and standards of care, making the future findings more generalizable. To minimize bias in this open  
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22 blinded trial, the study design incorporates central adjudication of meaningful outcomes, such as  
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24 death and hospital admissions (nonfatal MI or HF), by an independent committee blinded to  
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26 treatment. REBOOT has been judged a highly pragmatic trial by independent researchers assessing  
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28 trial design in Europe.<sup>27</sup>  
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34 An important aspect related to the benefits of  $\beta$ -blockers in different cardiovascular  
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36 conditions, such as MI and HF, is the type and dose of agent. In the context of HF, a head to head  
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38 comparison showed that not all  $\beta$ -blockers have the same clinical benefits.<sup>28</sup> In this trial, the selection  
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40 of the type and dose of  $\beta$ -blocker agent is decided by the treating physician. On randomization and  
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42 on each follow-up, the type and dose of  $\beta$ -blocker agent will be recorded. Despite the statistical power  
43  
44 will be limited, recording these data will allow an exploratory analysis on the potential differences  
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46 between different  $\beta$ -blocker strategies (type of agent and % of target dose prescribed).  
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53 The current SARS-Cov-2 virus pandemic (COVID-19 disease) have had an impact in MI  
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55 admissions and outcomes, as well as a potential emotional impact on patients already enrolled in the  
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57 trial.<sup>29</sup> In our last amendment to the protocol, a brief questionnaire concerning COVID-19 was  
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59 included in all telephone follow-ups. Similarly, COVID-19 had an impact on the pace of recruitment  
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4 but enrollment was not stopped. It should be noted the outstanding commitment from all investigators  
5 and hospitals to the study, since despite the massive burden associated with the pandemic,  
6 participation in the trial went on. As in July 2021, REBOOT trial has recruited 5,000 patients already  
7 (59% of target population). Taking into consideration the reduction of the recruitment pace during  
8 the worst stages of the pandemic, it is expected that total sample size will be recruited before the end  
9 of 2022.  
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18 Several potential limitations need to be considered. The lack of a placebo introduces a  
19 theoretical risk of overestimation of the effect of  $\beta$ -blockers on patient-reported outcomes during  
20 follow-up, since no placebo effect can be subtracted from the results of the  $\beta$ -blocker arm. The  
21 pragmatic nature of the study increases the external validity and the potential for high generalizability  
22 and allows the study to be performed at relatively low cost; however, this comes at the cost of possible  
23 bias toward the null hypothesis because of a potentially high proportion of crossovers and possible  
24 difficulties in interpretation due to the non-homogeneity of drug and dose in the treatment arm. The  
25 study design also assumes a drug class effect. Patients with type 1 and type 2 MI are included in this  
26 trial despite some differences in the pathophysiology and prognosis are expected between them. This  
27 information should be taken into account when interpreting the results, though type 2 MI might  
28 represent be a minority. Heart rate achieved on  $\beta$ -blocker therapy is a good physiological marker of  
29 compliance and dose-adequacy. Unfortunately, given the pragmatic nature of the trial, heart rate  
30 during follow-up is not recorded.  
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## 50 Conclusions

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52 The REBOOT trial is a pragmatic, controlled, prospective, randomized, open-label blinded  
53 endpoint clinical trial testing the benefits of  $\beta$ -blocker therapy in patients discharged after an MI with  
54 LVEF >40% and managed according to state-of-the art practice. Differences in incidence rate for the  
55 composite of all-cause death, nonfatal reinfarction, or HF hospitalization will be assessed for a median  
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follow-up period of 2.75 years. The results of the REBOOT trial will provide strong evidence for  
guiding the clinical treatment of patients surviving myocardial infarction.



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## **Conflicts of interest**

None.

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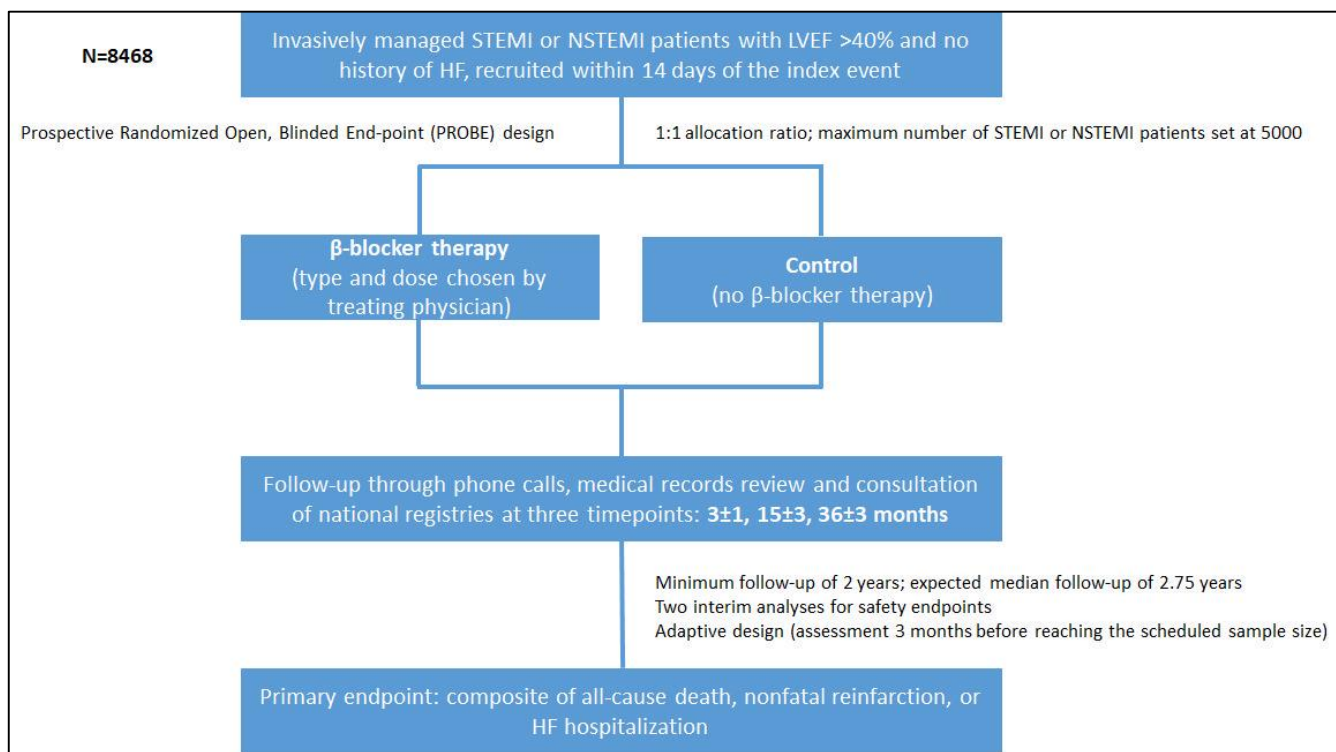
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4 **Figure Legends**  
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7 **Figure 1. REBOOT study flowchart**  
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4 **Figure 2.** Enrollment criteria  
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INCLUSION CRITERIA (all the following)
<ul style="list-style-type: none"><li>▪ Patients ≥18 y.o. admitted with a main diagnosis of acute MI, either STEMI or NSTEMI*.</li><li>▪ LVEF&gt;40% as evaluated by any imaging technique anytime during hospitalization. If more than one LVEF evaluation is performed, the one closest to discharge will prevail for inclusion purposes.</li><li>▪ Invasive management during index admission (regardless type of subsequent revascularization technique).</li><li>▪ Signed informed consent.</li></ul>
EXCLUSION CRITERIA (any of the following)
<ul style="list-style-type: none"><li>▪ Known allergy or intolerance to β-blockers.</li><li>▪ Absolute contraindication to β-blocker therapy according to treating physician.</li><li>▪ Prior history of HF or Killip class ≥II on admission or during hospitalization</li><li>▪ Severe valvular heart disease (&gt; 3+ for aortic or mitral regurgitation, aortic or mitral valve area ≤1.0 cm<sup>2</sup>).</li><li>▪ Any condition apart from acute MI requiring B-blocker prescription according the treating physician.</li><li>▪ Any medical condition that would seriously limit life expectancy (to below 1 year).</li><li>▪ Participation in another trial.</li></ul>

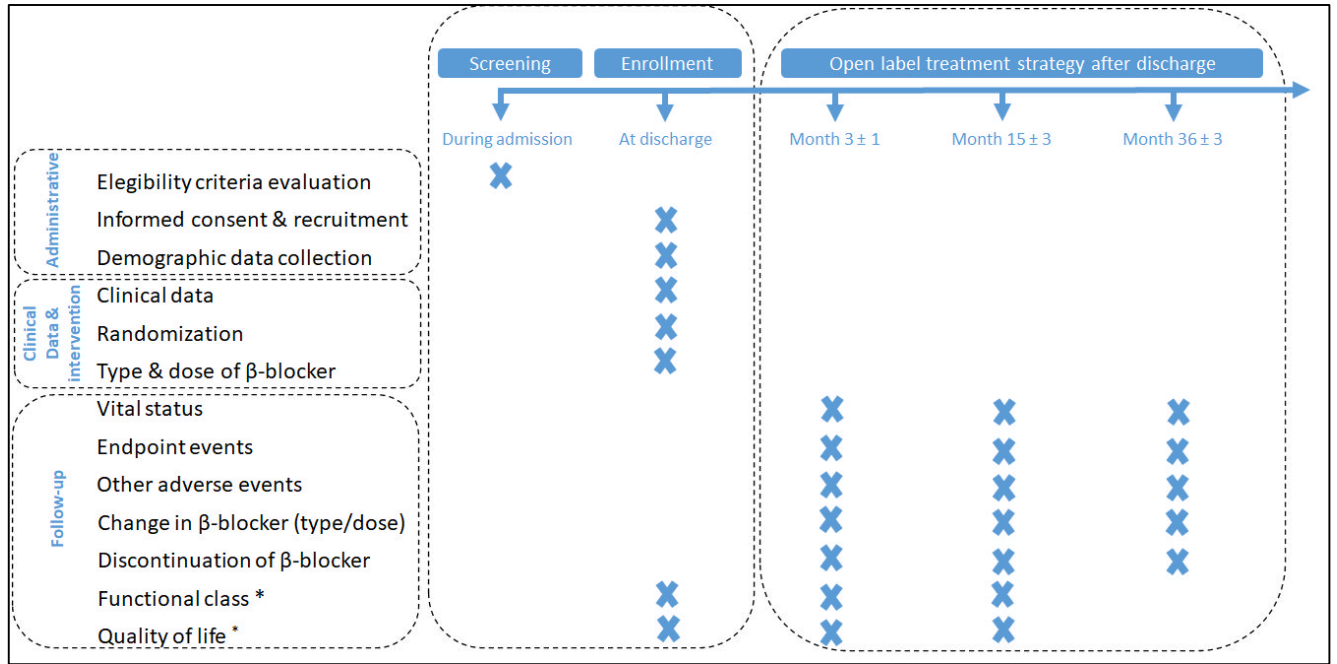
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55 *HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction;*  
56 *NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary*  
57 *intervention; STEMI, ST-segment elevation myocardial infarction.*  
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*\* The maximum number of STEMI or NSTEMI patients recruited is set at 5000. After recruitment of 5000 patients with one acute MI type, only patients with the other type will be recruited until the end of the study.*



**Figure 3. Study data collection**



\* limited to a sub-sample of  $\geq 1000$  patients

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4 **Figure 4. Study endpoints**  
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7 PRIMARY ENDPOINT
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SECONDARY ENDPOINTS
TERTIARY ENDPOINTS

CCS, Canadian Cardiovascular Society; EQ-5D, European Quality of Life-5 Dimensions.  
HF, heart failure; IIEF-5, International Index Erectile Function; NYHA, New York Heart  
Association; PHQ-2, Patient Health Questionnaire-2.

\* limited to a sub-sample of  $\geq 1000$  patients

**Figure 5. Pre-specified subgroups**

Type of acute MI	STEMI vs NSTEMI
Revascularization	Complete vs incomplete
Obstructive lesions	Acute MI with obstructive coronary lesions vs MINOCA
LVEF	41-49% vs $\geq 50\%$
Sex	Men vs women
Heart rhythm	Sinus rhythm vs atrial fibrillation
$\beta$ -blockers before admission	Yes vs no
In-hospital $\beta$ -blockers	Yes vs no
Hypertension	Yes vs no
Diabetes mellitus	Yes vs No
COPD	Yes vs no
Age	<75 vs $\geq 75$ y.o.

*COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.*

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4 **APPENDIX**

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6 **ANNEX I. Full list of investigators/collaborators:**

7  
8 Abel Andres; Adriano Autieri; Albert Ariza; Alberto Cordero; Alessandra Costalunga; Alessandro  
9 Navazio; Alessandro Sionis; Alfonso Torres; Alfonso Valle; Alfredo Bardaji; Alfredo Renilla; Alina  
10 Oлару; Ana García-Alvarez; Ana Maria Campos; Angel Perez-Rivera; Annalisa Aloisi; Antonio  
11 Bayes-Genis; Antonio Ignacio Fernández Ortiz; Antonio Rizzo; Barbara Coutsoumbas; Beatrice  
12 Mariottoni; Camilla Renèe Zawaideh; Carlos Gonzalez-Juanatey; Carlos Tomás Querol; Carmen  
13 Rus; Claudio Vimercati; Danilo Saverio Vetrano; Delicia Gentile; Eduardo Alegría; Eduardo  
14 Arroyo; Eduardo Moreno Escobar; Efrén Martínez-Quintana; Elena Martinoli; Elvira Marco; Enrica  
15 Vitale; Enrico Nicolis; Erika Gazzola; Ezio Mesolella; Felipe Navarro; Francesco Manca; Francisco  
16 Fernández-Aviles; Francisco Marin-Ortuño; Francisco Torres; Gabriel Vázquez-Oliva; Gian Piero  
17 Perna; Gianni Casella; Giovanni Sirianni; Giuletta Grigis; Giulia Bugani; Giulia Pongetti; Giuseppe  
18 Di Tano; Gonzalo Navarrete; Hector Bueno; Hugo Paris; Ines Moeller; Isidro Hernandez; Ivana  
19 Pariggiano; J. Alberto San Román; Javier Botas; Jordi Palet; Jorge Sanchez; Jose A. Ramirez; José  
20 Angel Cabrera; José Díaz; José Manuel García Ruiz; Jose R Gonzalez-Juanatey; Jose Rozado; Josep  
21 Maria Alegret; Juan C García Rubira; Juan Luis Bonilla; Juan Ruiz-García; Juan Sanchis; Julio  
22 Hernandez; Lorenzo Calò; M<sup>a</sup> Jesus Rollan; Manuel de Mora; Marco Solari; Maria Giulia Perrelli;  
23 Maria Rosa de Iacono; Mariachiara Buffa; Mario Lombardi; Matteo Bianco; Mauro Rondi; Natale  
24 Brunetti; Nicoletta De Cesare; Nicoletta De Santis; Oscar Diaz; Oscar Fabregat-Andres; Pablo Bazal;  
25 Pedro Morillas; Petra Sanz; Pierangelo Basso; Ricardo Ieva; Roberto Carletti; Roberto Martin;  
26 Roman Freixa; Rosa Fernandez; Rosario Ortas; Sabina Meloni; Stefano Tondi; Valentina Regazzoni;  
27 Vicente Mora; Agustín Martín García; Alba Cervero; Alba Martin; Albert Duran Cambra; Albert  
28 Massó- van Roessel; Alberto Pérez ; Alberto Pullara; Albina Aldomà; Alejandro Amador; Alejandro  
29 Junco; Alejandro Pascual; Alejandro Rodriguez; Alejandro Sanchez Grande-Flecha; Alejandro  
30 Villanueva; Alice Vitagliano; Alicia Bautista Pavés; Alicia Gainza; Alicia Moreno; Alvaro Aceña;  
31 Alvaro Vicedo; Ana Elvira Laffond; Ana Isabel Santos; Ana María Moralejo; Ana Merino; Ana M  
32 Pello-Lázaro; Ana Portoles; Ana Roman; Ana Testa; Ana Ayesta; Andrea Cafro; Andrea Chiampan;  
33 Andrea Finzi; Andrea Kallmeyer; Andrea Lopez; Andrea Rubboli; Andrea Veliz; Andrés Iñiguez;  
34 Andres Morist; Ane Aboitiz; Angel Franch; Angela Alonso; Angela Juez; Angelica Romero; Anna  
35 Carrasquer; Antonella Vasamì; Antoni Perelló-Bordoy; Antonia Sambola; Antonio Gamez; Antonio  
36 Jesus Martín; Antonio Lara-Padrón; Antonio Miñano; Antonio Piñero; Antonio Quesada; Antonio  
37 Tello; Aritz Gil; Armando Perez; Arturo Lanaspá; Aurora Diaz; Beatriz de Tapia Majado; Beatriz  
38 Saiz; Beatriz Samaniego; Beatriz Sampedro; Belen Alvarez; Belen Prado; Berenice Caneiro;  
39 Bernardo Ayala Borges ; Berta Vega; Betel Olaizola; Blanca Olivares; Carla Jimenez; Carlos  
40 Baladrón; Carlos Galán; Carlos Miguíto; Carlos Millan Rodriguez; Carlos Ortiz; Carmen Guerrero;  
41 Carmen Palacios; Carolina Hernández-Luis; Carolina Redondo; Carolina Sorto; Cecilia Corros;  
42 Cecilia Lopez; Charo Cortina; Chiara Angeletti; Claudia Santos; Clea Gonzalez; Conchita Oliva;  
43 Cosme García; Cristina Cambeiro; Cristina Sanchez-Enrique; Cristina Tapia; Damaris de Sousa;  
44 Daniele Grosseto; Daniele Nassiacos; David Gomez; David Rutigliano; David Vivas; Deborah  
45 Cosmi; Diego Arroyo; Dolores Ruiz Fernández; Eduardo Caballero; Eduardo Zatarain; Elena  
46 Barbaresi; Elena Batlle; Elena España; Elena Lopez; Elena Tundidor; Elene Saez de Buruaga;  
47 Elisabeth Fernandez; Eliu David; Elizabet Méndez Eirín; Emad Abu Assi; Emanuela Clara Bertolino;  
48 Emilia Blanco; Enrico Cerrato; Enrico Gotti; Enrique Iglesias Río; Enrique Leon; Enrique Sanchez;  
49 Ernesto del Amo; Ernesto Hernandez; Esmeralda Capin; Ester Sánchez-Corral; Eugenio Vilei; Eva  
50 Gonzalez; Eva Santamaria; Eva Santamaria; Fabrizio Poletti; Federica del Giudice; Felice Achilli;  
51 Fernando Arribas; Filippo Maria di Dona; Flor Baeza; Francesca Pietrucci; Francisco José Pastor;  
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4 Francisco Manuel Burillo; Francisco Rivera; Fco Jesus Gonzalez; Gabriel Hurtado; Gabriel Sanchez;  
5 Gabriella Foresti; Gaspar Melis; Gerard Oristrell; Gian Battista Danzi; Giancarlo Piovaccari;  
6 Gianfranco Pistis; Gil Bonet; Giovanni Tortorella; Gislaïne Castilho de Oliverira; Gonzalo Martin;  
7 Guillermo Moreno; Hector García; Hernan Tajés; Iciar García; Iciar Piedra; Idaira Famara  
8 Hernandez-Baldomero; Ignacio Sanchez; Inés García Lunar; Inmaculada Fernandez; Irene Buera;  
9 Irene Sempere; Irene Toribio; Iria Martinez; Iria Silva; Iris Garrido; Isabel Hernández; Itsaso  
10 Larrabide; Ivan Olavarri; Jairo Monedero; Jaume Pons; Javier Borrego; Javier Castrodeza; Javier  
11 López Díaz; Javier Mailló; Javier Mendoza; Javier Rekondo; Javier Simón; Javier Tobar; Javier  
12 Zueco; Jean Paul Vilchez Tschischke; Jessica Roa; Jessica Vaquero; Jessika Gonzalez; Jesus  
13 Carmona; Jesús Molina; Jesus Zarauza; José Ángel Rodríguez Fernández; Jose Enrique Romero; Jose  
14 Javier Sanchez; Jose Juan Jimenez; Jose Manuel Vazquez; Jose Miguel Rivera-Caravaca; Jose Seijas  
15 Amigo; Jose Tuñón; Josefa García; Juan Carlos Muñoz; Juan Escudero; Juan Franco; Juan Martínez  
16 Milla; Juan Ocampo Miguez; Julia Gonzalez; Julio Echarte; Laura Alvarez; Laura de la Fuente  
17 Blanco; Laura García; Laura Montagna; Laura Pertejo; Laura Rodríguez Sotelo; Leire Goikolea;  
18 Leire Goñi; Lidia Martinez; Lorena Garcia Riesco; Lucía Matute-Blanco; Lucía Pérez Cebey; Lucia  
19 Rioboo Leston; Luis Cerdán; Luis de la Fuente-Galán; Luis Martinez; Luis Ruiz Guerrero; Luna  
20 Carrillo; Luna Carrillo; M<sup>a</sup> Asun Esteve; Magdalena Carrillo; Manel Sabate; Manuel Iglesias; Manuel  
21 Jesús Gómez; Manuel Lobo; Manuel Lopez; Marco Ruozzi; Marcos Farrais; Maria Alessandra Puteo;  
22 María del Carmen Gómez Rubín; Maria Facenda; Maria García; María Garrido; Maria Giovanna  
23 Pallotti; Maria Isabel Ezpeleta; Maria Jesus García; Maria Jose Antolinos; Maria Lasala; María López  
24 Alvarez; María López Benito; Maria Luisa Rodriguez; María Martín Mariscal; Maria Melendo; María  
25 Molina; Maria Ramos; Maria Rivadeneira; Maria Teresa Perez; Maria Vittoria Matassini; Mariam  
26 Quintanilla; Maribel Gonzalez; Marina Oliver; Marina Revilla; Marta Alonso-Fernández-de-Gatta;  
27 Marta Fernández; Marta Lopez; Marta Martin-Cabeza; Marta Monteagudo; Marta Santisteban; Marta  
28 Torres; Marta Torres; Massimo Piepoli; Matteo Azzarone; Matteo Lisi; Maurizio Mangiavacchi;  
29 Meryem Ezzitoun; Miguel Angel Arnau Arnau; Miguel Lapeña; Miguel Molina; Miguel Puentes;  
30 Miguel Soroa; Mikel Martinez; Miquel Vives; Miriam Salim; Nacho Hernandez; Nadia Mollichelli;  
31 Nelva Sosa; Niccolò Simonelli; Nicola Locuratolo; Nieves Romero; Noelia Rojo-Prieto; Noemi  
32 Barja; Norberto Herrera Gómez; Nuria Sánchez; Olatz Zaldua; Onofre Caldes; Oriol De Diego; Oriol  
33 Rodriguez; Oscar González; Oscar M. Peiró; Oscar Vedia; Pablo Gil; Pablo Jorge-Pérez; Pablo  
34 Manuel Fernández; Pablo Jover-Pastor; Pablo Martinez; Pablo Pastor; Paloma Avila; Paolo  
35 Sganzerla; Pasquale Baratta; Pasquale Caldarola; Patricia Arenas; Pau Rello; Paula García; Paula  
36 Menendez; Pedro Luis Dorado; Pedro Martin; Pedro Vigil; Rafa Bourio; Rafael Cobas; Rafael  
37 Hidalgo; Rafael Moscicki; Ramon Andion; Ramon Rios; Raquel Díaz Muñoz; Raquel Marzoa;  
38 Raymundo Ocaranza; Roberto Martin; Rocío Barquero; Rocio Ruiz; Rodrigo Fernandez; Roi  
39 Bangueses; Romina Navarri; Rosa Agra; Rosa Sanchez; Ruben Bergel; Ruth Sanchez; Sandra Gómez  
40 Talavera; Santiago García-Mancebo; Sergio Cardenas; Sergio Huertas; Sergio Huertas; Silvia  
41 Bayona; Silvia Gopar; Silvia Lozado-Edo; Silvia Mera; Silvia Prieto; Silvia Stabellini; Simona  
42 D'Orazio; Sonia Santos; Susana Martinez Huertas; Tamara Fernández; Tamara García; Tania Seoane;  
43 Tania Seoane García; Teresa Simón; Toni Soriano; Ugo Limbruno; Valentina Pelizzoni; Valerio  
44 Epureanue; Vanesa Alonso; Verónica Artiaga; Vicente Bertomeu-Gonzalez; Vicente Peral; Víctor  
45 Donoso; Víctor Perez; Víctor Puebla Rojo; Victoria Espejo; Victoria Platero; Virginia Mass; Walter  
46 Bragagnini; Xurxo Martinez; Yolanda Gallego; Yvan Persia.  
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4 **ANNEX II. Full list of participating centers (alphabetical order):**  
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- 6 1. Alto del Guadalquivir;
- 7 2. Alvarez Buylla;
- 8 3. Arcispedale S. Maria Nuova, Reggio Emilia;
- 9 4. Arnau de Vilanova de Lleida;
- 10 5. Arquitecto Macide, Ferrol;
- 11 6. Basurto;
- 12 7. Bellvitge;
- 13 8. Bolognini, Serrate;
- 14 9. Burgos;
- 15 10. C.G.Morgagni, Forlì;
- 16 11. Cabueñes, Gijón;
- 17 12. Centro Nacional de Investigaciones Cardiovasculares (CNIC);
- 18 13. CHUAC Coruña;
- 19 14. CHUS, Santiago;
- 20 15. CHUVI Vigo;
- 21 16. Civile di Baggiovara;
- 22 17. Civile di Legnano;
- 23 18. Clinic Barcelona;
- 24 19. Clínico de Valencia;
- 25 20. Clínico de Valladolid;
- 26 21. Clinico San Carlos;
- 27 22. Complejo Universitario de Canarias;
- 28 23. Complejo Universitario Insular Materno Infantil;
- 29 24. Consorci Sanitari Integral;
- 30 25. Cremona;
- 31 26. Denia;
- 32 27. Desio;
- 33 28. Doce de Octubre;
- 34 29. Doctor Peset;
- 35 30. Fundación Alcorcón;
- 36 31. Fundación Althaia de Manresa;
- 37 32. Fundación Jimenez Díaz;
- 38 33. Galdakao Usansolo;
- 39 34. General de La Palma
- 40 35. General de Villalba;
- 41 36. General universitario de Elche;
- 42 37. General Universitario de Elda;
- 43 38. Germans Trias i Pujol;
- 44 39. Gran Canaria Doctor Negrín;
- 45 40. Gregorio Marañón;
- 46 41. Gualdo Tadino - Gubbio;
- 47 42. Guglielmo da Saliceto, Piacenza;
- 48 43. HUCA Oviedo;
- 49 44. IMED Valencia;
- 50 45. Infanta Elena Valdemoro;
- 51 46. Infermi di Rimini;

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- 4 47. Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan;
- 5 48. Joan XXIII Tarragona;
- 6 49. Juan Ramón Jiménez, Huelva;
- 7 50. La Fe Valencia;
- 8 51. La Luz;
- 9 52. León;
- 10 53. Della Misericordia, Grosseto;
- 11 54. Lluís Alcanyis, Xativa;
- 12 55. Lucus Augusti, Lugo;
- 13 56. Maggiore di Bologna;
- 14 57. Marqués de Valdecilla, Santander;
- 15 58. Miguel Servet, Zaragoza;
- 16 59. Montecelo Pontevedra;
- 17 60. Navarra;
- 18 61. Nuestra Señora Candelaria;
- 19 62. Policlinico San Marco - Osio Sotto;
- 20 63. Presidio Ospedaliero di Passirana;
- 21 64. Presidio Ospedaliero di Saronno;
- 22 65. Quirón Pozuelo;
- 23 66. Regional Carlos Haya, Malaga;
- 24 67. Reina Sofía Córdoba;
- 25 68. Rey Juan Carlos Mostoles;
- 26 69. Río Hortega Valladolid;
- 27 70. Riuniti di Ancona;
- 28 71. Riuniti Foggia;
- 29 72. Ruber Internacional;
- 30 73. Ruber Juan Bravo;
- 31 74. Sacro Cuore Don Calabria, Negrar;
- 32 75. San Agustín, Aviles;
- 33 76. San Cecilio, Granada;
- 34 77. San Juan de Alicante;
- 35 78. San Juan de la Cruz, Ubeda;
- 36 79. San Luigi Gonzaga;
- 37 80. San Paolo di Bari;
- 38 81. Sant Joan de Reus;
- 39 82. Santa Creu i Sant Pau;
- 40 83. Santa Lucía Cartagena;
- 41 84. Santa Maria delle Croci, Ravenna;
- 42 85. Sant'Anna e San Sebastiano di Caserta;
- 43 86. Santi Antonio e Biagio di Alessandria;
- 44 87. Son Espases Mallorca;
- 45 88. Teknon;
- 46 89. Torrejón;
- 47 90. Torrevieja;
- 48 91. Treviglio;
- 49 92. Txagorritxu;
- 50 93. Universitario de Jaen;
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- 94. Universitario de Salamanca;
- 95. Vaio, Fidenza;
- 96. Valdichiana Santa Margherita, Cortona;
- 97. Vall d´Hebron;
- 98. Verge de la Cinta;
- 99. Veris Delli Ponti, Scorrano;
- 100. Villa Sofia, Palermo;
- 101. Vinalopo;
- 102. Virgen de la Arrixaca, Murcia;
- 103. Virgen de la Macarena, Sevilla;
- 104. Virgen de las Nieves, Granada;
- 105. Virgen de los Lirios, Alcoy;
- 106. Virgen del Rocío Sevilla;
- 107. Vizzolo Predabissi, Melegnano.