# Rationale and design of the pragmatic clinical trial *tREatment with Beta-blockers after myOcardial infarction withOut reduced ejection fracTion* (REBOOT)

Xavier Rossello[1,2,3]*, MD PhD; Sergio Raposeiras-Roubin[1,4]*, MD, PhD; Roberto Latini[5], MD PhD; Alberto Dominguez-Rodriguez[3,6], MD PhD; José A Barrabés[3,7], MD PhD; Pedro L Sánchez[3,8], MD PhD; Manuel Anguita[9], MD PhD; Felipe Fernández-Vázquez[10], MD PhD; Domingo Pascual-Figal[1,3,11], MD PhD; José M De la Torre Hernandez[12], MD, PhD; Stefano Ferraro[13], MD; Alfredo Vetrano[14], MD; José A. Pérez-Rivera[15], MD, PhD; Oscar Prada-Delgado[16], MD; Noemí Escalera[1], BPT; Lidia Staszewsky[5], MD; Gonzalo Pizarro[1,3,17], MD PhD; Jaume Agüero[3,18], MD PhD; Stuart Pocock[19], PhD; Filippo Ottani[20], MD PhD; Valentín Fuster[1,21], MD PhD; Borja Ibáñez[1,3,22], MD PhD; REBOOT-CNIC investigators†.

From:

*[1]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; [2]Cardiology Department, Hospital Universitari Son Espases - IDISBA, Palma de Mallorca, Spain; [3]CIBER de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain. [4]Cardiology Department, University Hospital Álvaro Cunqueiro, Vigo, Spain; [5] Department of Cardiovascular Medicine. Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy; [6] Servicio de Cardiología, Hospital Universitario de Canarias, Tenerife, Spain; [7] Department of Cardiology, Hospital Universitari Vall d'Hebron, Universitat Autònoma, Barcelona, Spain; [8] Cardiology Department, University Hospital of Salamanca, Biomedical Research Institute of Salamanca (IBSAL), Salamanca, Spain [9] Department of Cardiology, Hospital Universitario Reina Sofía de Cordoba, Córdoba, Spain; [10]Cardiology Department, Hospital Universitario de León, León, Spain; [11] Cardiology Department, Hospital Virgen de la Arrixaca, IMIB-Arrixaca and University of Murcia, Murcia, Spain; [12] Cardiology Department, Hospital Marques de Valdecilla, Santander, IDIVAL, Spain; [13]Cardiology Department, Ospedale Guglielmo da Saliceto, Piacenza, Italy; [14]Cardiology Department, Ospedale S. Anna e S. Sebastiano, Caserta, Italy; [15]Department of Cardiology, Hospital Universitario de Burgos, Burgos, Spain; [16]Department of Cardiology, Hospital Universitario A Coruña, A Coruña, Spain; [17]Cardiology Department, Hospital Ruber Juan Bravo Quironsalud UEM, Madrid, Spain;*

*[18]Cardiology Department, Hospital Universtitari i Politecnic La Fe, Valencia, Spain; [19]London School of Hygiene & Tropical Medicine, London, UK; [20]Cardiology Department, Ospedale Vizzolo Predabissi di Melegnano, Milan, Italy; [21]Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, NY, USA; [22]IIS-Fundación Jiménez Díaz University Hospital.*

* equal contributors.

† Full list of investigators/collaborators can be found in Annex I

**Corresponding author:**

**Borja Ibanez**. MD PhD. Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) & IIS-Fundación Jiménez Díaz University Hospital. c/ Melchor Fernandez Almagro, 3. 28029 Madrid (Spain). Email: bibanez@cnic.es

## Abstract

**Background.** There is a lack of evidence regarding the benefits of β-blocker treatment after 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 β-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 β-blocker therapy (agent and dose according to treating physician) or no β-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 β-blockers to patients discharged after MI without reduced LVEF.

## Keywords

β-blockers; acute myocardial infarction; left ventricular ejection fraction; randomized clinical trial.

## Introduction

The clinical benefit of β-blockers after a myocardial infarction (MI) in patients with reduced left ventricular ejection fraction (LVEF) is supported by solid evidence from modern trials.[1-3] However, the evidence for prescribing β-blockers after an uncomplicated MI in patients with LVEF >40% is less well established.[4] With the exception of the CAPRICORN trial,[5] which only recruited patients with LVEF ≤40%, all randomized clinical trials testing the benefits of post-MI β-blocker maintenance were performed in the pre-reperfusion era. Pooled data showed that post-MI β-blocker therapy reduced the risk of death by 23% (95%CI 15-31%) over a 2-year follow-up,[1] 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).[6] Systematic early angiography and revascularization has also massively reduced the incidence of adverse events after non-ST elevation MI (NSTEMI).[7] 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,[8] most post-MI patients are prescribed potent antithrombotics, statins, and other agents that improve prognosis.[9] 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.[10] Together, these diagnostic and therapeutic improvements have had a massive impact in the survival of post-MI patients.[11] Within this changing scenario, the clinical benefit of β-blockers after uncomplicated MI is a long-standing clinical question.[12]

In the absence of prospective randomized trials, attempts to evaluate the clinical benefit of β-blockers after MI in patients without reduced LVEF have shown conflicting results, and the observational nature of the data prohibits conclusions about causality.[3, 13-18] Clinical practice guidelines of both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) strongly recommend β-blockers for post-AMI patients with LVEF ≤40% (class IA).[9, 19-21] While recognizing gaps in evidence and the need for further research, both scientific societies also generally advocate the use of β-blockers in patients with LVEF >40%.[9, 21] Consequently, β-blockers are today given to a high proportion of post-MI patients without reduced LVEF, reaching >80% of patients in some cases.[22]

The lack of prospective clinical trials in the reperfusion era examining the effect of β-blockers in post-MI patients with LVEF > 40%, together with the drop in mortality linked to the introduction of evidence-based medications, calls for a definitive randomized clinical trial addressing this highly relevant clinical question.

## 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 (β-blocker therapy, where the type and dose will be determined by the managing physician) or the control group (lack of β-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 β-blocker therapy on a composite measure of mortality and morbidity in post-MI patients with LVEF >40%. The hypothesis is that post-discharge β-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.

The secondary endpoints are the ability of β-blocker therapy to reduce the risk of i) each of the primary endpoint measures separately (all-cause mortality, nonfatal reinfarction and HF admission); ii) cardiac death; and iii) malignant ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest).

## Study population

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

## Randomization and study intervention

All patients must provide written informed consent prior to randomization. Afterwards, patients will be centrally randomized via web or dedicated mobile app according to a permuted-block design with random varying blocks of 4, 6, and 8 subjects, stratified by recruiting center. After randomization, patients allocated to β-blocker therapy will receive the agent and dose chosen by their treating physician. Given the pragmatic nature of the trial and that β-blocker therapy after MI is

current common practice, the study will not provide any medication to participants. The recruiting centers are listed in the **Appendix**.

The only reason for patient withdrawal from the study is their desire to be excluded from the trial. The primary study endpoint will be assessed on an intention-to-treat (ITT) basis, and patients will therefore be assessed according to randomization, without regard for crossovers. Crossovers will remain in the trial, and follow-up will per protocol. However, the rate of and reasons for crossover will be recorded, and post-hoc analyses will consider only those patients adhering to the original randomization arm throughout follow-up.

## Follow-up and study outcomes

An overview of data collection during screening, enrollment, and treatment follow-up to study-end is shown in **Figure 3**. Follow-up monitoring will take place at three timepoints after enrollment (3±1, 15±3, 36±3 months) and will consist of phone calls, medical records review, and consultation of national registries, if needed. After identifying a potential event, the local investigator will collect and send the relevant information to the Clinical Trials Coordination Unit for blind adjudication by an independent committee. Follow-up will be for a minimum of 24 months and a maximum of 36 months (expected median follow-up is 2.75 years, assuming a constant inclusion rate). Two years after the last patient enrollment, all patients who have not reached the 36 months follow-up will be contacted for a final follow-up assessment.

The primary endpoint is the composite of all-cause death, nonfatal reinfarction, or HF hospitalization. Secondary endpoints will be i) individual primary endpoint components; ii) cardiac mortality; and iii) malignant arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest).

A sub-sample of ≥1000 consecutive patients will be invited to participate in the analysis of a tertiary endpoint assessing quality of life and functional class. Patients agreeing to participate in this

sub-study will be interviewed to determine their functional class (New York Heart Association and Canadian Cardiovascular Society class) and to complete the European Quality of Life-5 Dimensions (EQ-5D) questionnaire at 3 different timepoints: baseline (on enrollment) and at 3- and 15-month follow-up. The primary, secondary, and tertiary endpoints are described in **Figure 4.**

## Sample size calculation

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

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

## Safety analysis and stopping rules

Interim analyses will be performed on the primary and the secondary safety endpoints when 33% (240) and 66% (480) of events have been adjudicated. The interim analyses will follow the same statistical plans as the final analysis. Stopping guidelines for efficacy analysis will be based on the statistical Haybittle-Peto approach. Stopping guidelines for safety data are not predefined and will be left to the discretion of the DSMB. The trial will not be stopped in case of futility, as this outcome would be considered clinically relevant.

## Statistical analysis

The null hypothesis is that the rate of the primary endpoint (composite of all-cause death, nonfatal reinfarction, or HF hospitalization over a minimum 2 years of follow-up) will be the same in the β-blocker arm and the control group. The alternative two-sided hypothesis is that the rate of the primary endpoint in the β-blocker group will be either greater or smaller than the rate in the control group. Cumulative incidence for each treatment group will be assessed and plotted with the Kaplan-Meier method, and will be compared using the log-rank test, followed by the multivariable Cox proportional hazards model. Treatment effect will be estimated with hazard ratios (HR) and corresponding 95% confidence intervals. Due to the randomization process and the large sample size in the trial, we do not expect major covariate imbalances between treatment groups. However, for exploratory purposes, standardized differences will be calculated, and known prognostic factors presenting an imbalance higher than 0.1 standardized difference will be included in the multivariable Cox model. For all tests, 2-sided p-values with an alpha $\leq 0.05$ level of significance will be used.

Secondary endpoints will be assessed according to the same statistical analysis plan as the primary endpoints. The primary statistical analysis will be conducted according to the ITT principle. A per protocol (PP) secondary analysis will be performed (patient follow-up time truly on β-blockers or not).

## Pre-specified subgroup analyses

A set of 12 pre-specified subgroup analyses will be undertaken using interaction models based on the primary analysis model. These analyses will include the subgroup factor and the treatment subgroup interaction factor as covariates. Estimates will be presented as hazard ratios for each subgroup alongside their p-value for interaction. Pre-specified subgroups are listed in **Figure 5.**

## Discussion

The REBOOT trial aims to fill the existing knowledge gap on the efficacy of post-MI β-blocker therapy in patients with LVEF > 40% and treated according to the state-of-the-art.[12] This randomized clinical trial will update the scientific evidence for the use of β-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 β-blocker therapy vs. no β-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.[23] 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.[24] 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 β-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.[7, 12, 22] There is therefore a need for a new scientific evaluation of the potential benefits and harms of β-blockers in the context of current clinical practice. The only available evidence in this context comes from observational studies and registries,[3, 13-17] which have major limitations.[18] A common feature of all these observational studies based on real life practice is the very high prescription rate for β-blockers (>80%). However, it is noteworthy that prescription of β-blockers has slightly decreased in recent years. In a recent Danish Nationwide registry,[17] the proportion of patients with a first MI that were discharge on β-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 β-blockers after an acute MI is around 80%.[25] In any case, the very high proportion of β-blocker prescription implies a very high risk of bias. In particular, when the

prescription of a therapy is non-random and is instead based on patients' clinical characteristics, this creates the conditions for "confounding by indication", especially when these patient characteristics are associated with the clinical outcome. Randomization is needed to ensure that individuals with identical characteristics can be observed in both states, a condition lacking in all of these studies. The only way to resolve the question of the benefits of post-MI β-blocker therapy is to conduct adequately sized clinical trials.

REBOOT is a pragmatic trial very close to real life and thus have few exclusion criteria. Be on β-blockers before or take them during index hospitalization do not disqualify for the trial. While we anticipate that not many patients will be on maintenance β-blockers before enrollment, half of these will be randomized to no β-blocker therapy. Withdrawal of maintenance β-blockers might have an impact on events. In order to capture this potential effect, we set-up two actions: to establish the first follow-up early (i.e. 3 months after enrollment) to collect data related to any potential withdrawing consequences; and to pre-specify two subgroup analyses (see Figure 5), addressing this issue: prior (before admission) vs no prior therapy with beta blockers; and in-hospital use vs lack of in-hospital use of beta blockers.

To our knowledge, there are three ongoing clinical trials evaluating the effect of β-blockers in patients discharged after MI without reduced LVEF: the BEtablocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI) (NCT03646357); the Evaluation of Decreased Usage of Betablockers After Myocardial Infarction in the SWEDEHEART Registry (REDUCE-SWEDEHEART) (NCT03278509); and the Danish Trial of Beta Blocker Treatment After Myocardial Infarction Without Reduced Ejection Fraction (DANBLOCK) (NCT03778554).[26] The similarity of patient characteristics and some endpoints across these trials offers the opportunity to address relevant secondary questions in future individual-patient meta-analyses including close to 20,000 randomized patients. Researchers leading these trials have already begun discussions in this regard.

The REBOOT trial design places special emphasis on conducting a pragmatic clinical trial, for several reasons. First, post-MI β-blocker therapy is a low-cost intervention that forms part of routine clinical practice in a postmarketing phase of drug evaluation. Another factor is that a large sample size is needed to detect any potential treatment effect in a population with a declining cardiovascular event rate due to the widespread use of evidence-based treatments.[12] Moreover, unlike trials focused only on determining efficacy, which can overestimate benefits and underestimate harm, a pragmatic approach mimics real-world practice and increases the external validity of the findings. Our intervention is delivered as in normal practice, by regular staff using routinely available resources and standards of care, making the future findings more generalizable. To minimize bias in this open blinded trial, the study design incorporates central adjudication of meaningful outcomes, such as death and hospital admissions (nonfatal MI or HF), by an independent committee blinded to treatment. REBOOT has been judged a highly pragmatic trial by independent researchers assessing trial design in Europe.[27]

An important aspect related to the benefits of β-blockers in different cardiovascular conditions, such as MI and HF, is the type and dose of agent. In the context of HF, a head to head comparison showed that not all β-blockers have the same clinical benefits.[28] In this trial, the selection of the type and dose of β-blocker agent is decided by the treating physician. On randomization and on each follow-up, the type and dose of β-blocker agent will be recorded. Despite the statistical power will be limited, recording these data will allow an exploratory analysis on the potential differences between different β-blocker strategies (type of agent and % of target dose prescribed).

The current SARS-Cov-2 virus pandemic (COVID-19 disease) have had an impact in MI admissions and outcomes, as well as a potential emotional impact on patients already enrolled in the trial.[29] In our last amendment to the protocol, a brief questionnaire concerning COVID-19 was included in all telephone follow-ups. Similarly, COVID-19 had an impact on the pace of recruitment

but enrollment was not stopped. It should be noted the outstanding commitment from all investigators and hospitals to the study, since despite the massive burden associated with the pandemic, participation in the trial went on. As in July 2021, REBOOT trial has recruited 5,000 patients already (59% of target population). Taking into consideration the reduction of the recruitment pace during the worst stages of the pandemic, it is expected that total sample size will be recruited before the end of 2022.

Several potential limitations need to be considered. The lack of a placebo introduces a theoretical risk of overestimation of the effect of β-blockers on patient-reported outcomes during follow-up, since no placebo effect can be subtracted from the results of the β-blocker arm. The pragmatic nature of the study increases the external validity and the potential for high generalizability and allows the study to be performed at relatively low cost; however, this comes at the cost of possible bias toward the null hypothesis because of a potentially high proportion of crossovers and possible difficulties in interpretation due to the non-homogeneity of drug and dose in the treatment arm. The study design also assumes a drug class effect. Patients with type 1 and type 2 MI are included in this trial despite some differences in the pathophysiology and prognosis are expected between them. This information should be taken into account when interpreting the results, though type 2 MI might represent be a minority. Heart rate achieved on β-blocker therapy is a good physiological marker of compliance and dose-adequacy. Unfortunately, given the pragmatic nature of the trial, heart rate during follow-up is not recorded.

## Conclusions

The REBOOT trial is a pragmatic, controlled, prospective, randomized, open-label blinded endpoint clinical trial testing the benefits of β-blocker therapy in patients discharged after an MI with LVEF >40% and managed according to state-of-the art practice. Differences in incidence rate for the composite of all-cause death, nonfatal reinfarction, or HF hospitalization will be assessed for a median

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.

## Funding

REBOOT is a non-commercial trial whose main sponsor is the Spanish National Center for Cardiovascular Research (CNIC). The study also received partial funding from the BI group through the CIBERCV network.

## Acknowledgments

We thank the CNIC Clinical Trials Coordination Unit (CTCU), Computing Department, and administrative team for their outstanding support. Simon Bartlett provided English editing.

## Conflicts of interest

None.

## REFERENCES


1. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. Bmj 1999;**318**(7200):1730-7.

2. Martinez-Milla J, Raposeiras-Roubin S, Pascual-Figal DA, Ibanez B. Role of Beta-blockers in Cardiovascular Disease in 2019. Rev Esp Cardiol (Engl Ed) 2019;**72**(10):844-852.

3. Dahl Aarvik M, Sandven I, Dondo TB, Gale CP, Ruddox V, Munkhaugen J, Atar D, Otterstad JE. Effect of oral beta-blocker treatment on mortality in contemporary post-myocardial infarction patients: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2019;**5**(1):12-20.

4. Joo SJ, Kim SY, Choi JH, Park HK, Beom JW, Lee JG, Chae SC, Kim HS, Kim YJ, Cho MC, Kim CJ, Rha SW, Yoon J, Jeong MH, investigators K-Nr. Effect of beta-blocker therapy in patients with or without left ventricular systolic dysfunction after acute myocardial infarction. Eur Heart J Cardiovasc Pharmacother 2020.

5. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001;**357**(9266):1385-90.

6. Rossello X, Lobo-Gonzalez M, Ibanez B. Editor's Choice- Pathophysiology and therapy of myocardial ischaemia/reperfusion syndrome. Eur Heart J Acute Cardiovasc Care 2019;**8**(5):443-456.

7. Ibanez B, Raposeiras-Roubin S, Garcia-Ruiz JM. The Swing of beta-Blockers: Time for a System Reboot. J Am Coll Cardiol 2017;**69**(22):2721-2724.

8. Bueno H, Rossello X, Pocock S, Van de Werf F, Chin CT, Danchin N, Lee SW, Medina J, Vega A, Huo Y. Regional variations in hospital management and post-discharge mortality in patients with non-ST-segment elevation acute coronary syndrome. Clin Res Cardiol 2018;**107**(9):836-844.

9. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, Group ESCSD. 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**(2):119-177.

10. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology /American College of Cardiology /American Heart Association /World Heart Federation Task Force for the Universal Definition of Myocardial I. Fourth Universal Definition of Myocardial Infarction (2018). Circulation 2018;**138**(20):e618-e651.

11. Ibanez B, Heusch G, Ovize M, Van de Werf F. Evolving Therapies for Myocardial Ischemia/Reperfusion Injury. J Am Coll Cardiol 2015;**65**(14):1454-1471.

12. Rossello X, Pocock SJ, Julian DG. Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care. J Am Coll Cardiol 2015;**66**(11):1273-1285.

13. Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, Danchin N, Deanfield JE, Hemingway H, Fox KAA, Timmis AD, Gale CP. beta-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. J Am Coll Cardiol 2017;**69**(22):2710-2720.

14. Choo EH, Chang K, Ahn Y, Jeon DS, Lee JM, Kim DB, Her SH, Park CS, Kim HY, Yoo KD, Jeong MH, Seung KB. Benefit of beta-blocker treatment for patients with acute myocardial infarction and preserved systolic function after percutaneous coronary intervention. Heart 2014;**100**(6):492-9.

15. Raposeiras-Roubin S, Abu-Assi E, Redondo-Dieguez A, Gonzalez-Ferreiro R, Lopez-Lopez A, Bouzas-Cruz N, Castineira-Busto M, Pena Gil C, Garcia-Acuna JM, Gonzalez-Juanatey JR. Prognostic Benefit of Beta-blockers After Acute Coronary Syndrome With Preserved Systolic Function. Still Relevant Today? Rev Esp Cardiol (Engl Ed) 2015;**68**(7):585-91.

16. Puymirat E, Riant E, Aissoui N, Soria A, Ducrocq G, Coste P, Cottin Y, Aupetit JF, Bonnefoy E, Blanchard D, Cattan S, Steg G, Schiele F, Ferrieres J, Juilliere Y, Simon T, Danchin N. beta blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. BMJ 2016;**354**:i4801.

17. Holt A, Blanche P, Zareini B, Rajan D, El-Sheikh M, Schjerning AM, Schou M, Torp-Pedersen C, McGettigan P, Gislason GH, Lamberts M. Effect of long-term beta-blocker treatment following myocardial infarction among stable, optimally treated patients without heart failure in the reperfusion era: a Danish, nationwide cohort study. Eur Heart J 2021;**42**(9):907-914.

18. Desta L, Raposeiras-Roubin S, Ibanez B. The Art of Prescribing beta-Blockers After Myocardial Infarction. Circ Cardiovasc Interv 2021;**14**(4):e010720.

19. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;**127**(4):e362-425.

20. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine

MS, Smalling RW, Zieman SJ, American College of C, American Heart Association Task Force on Practice G, Society for Cardiovascular A, Interventions, Society of Thoracic S, American Association for Clinical C. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;**64**(24):e139-228.

21. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;**42**(14):1289-1367.

22. Goldberger JJ, Bonow RO, Cuffe M, Liu L, Rosenberg Y, Shah PK, Smith SC, Jr., Subacius H, Investigators O. Effect of Beta-Blocker Dose on Survival After Acute Myocardial Infarction. J Am Coll Cardiol 2015;**66**(13):1431-41.

23. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982;**247**(12):1707-14.

24. Norwegian Multicenter Study G. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;**304**(14):801-7.

25. Raposeiras-Roubin S, Abu-Assi E, Caneiro-Queija B, Cobas-Paz R, Rioboo-Leston L, Garcia Rodriguez C, Giraldez Lemos C, Blanco Vidal M, Ogando Guillan B, Perez Martinez I, Paredes-Galan E, Jimenez-Diaz V, Baz-Alonso JA, Calvo-Iglesias F, Iniguez-Romo A. Effect of beta-blocker dose on mortality after acute coronary syndrome. Rev Port Cardiol (Engl Ed) 2018;**37**(3):239-245.

26. Kristensen AMD, Bovin A, Zwisler AD, Cerquira C, Torp-Pedersen C, Botker HE, Gustafsson I, Veien KT, Thomsen KK, Olsen MH, Larsen ML, Nielsen OW, Hildebrandt P, Foghmar S, Jensen SE, Lange T, Sehested T, Jernberg T, Atar D, Ibanez B, Prescott E. Design and rationale of the Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction: study protocol for a randomized controlled trial. Trials 2020;**21**(1):415.

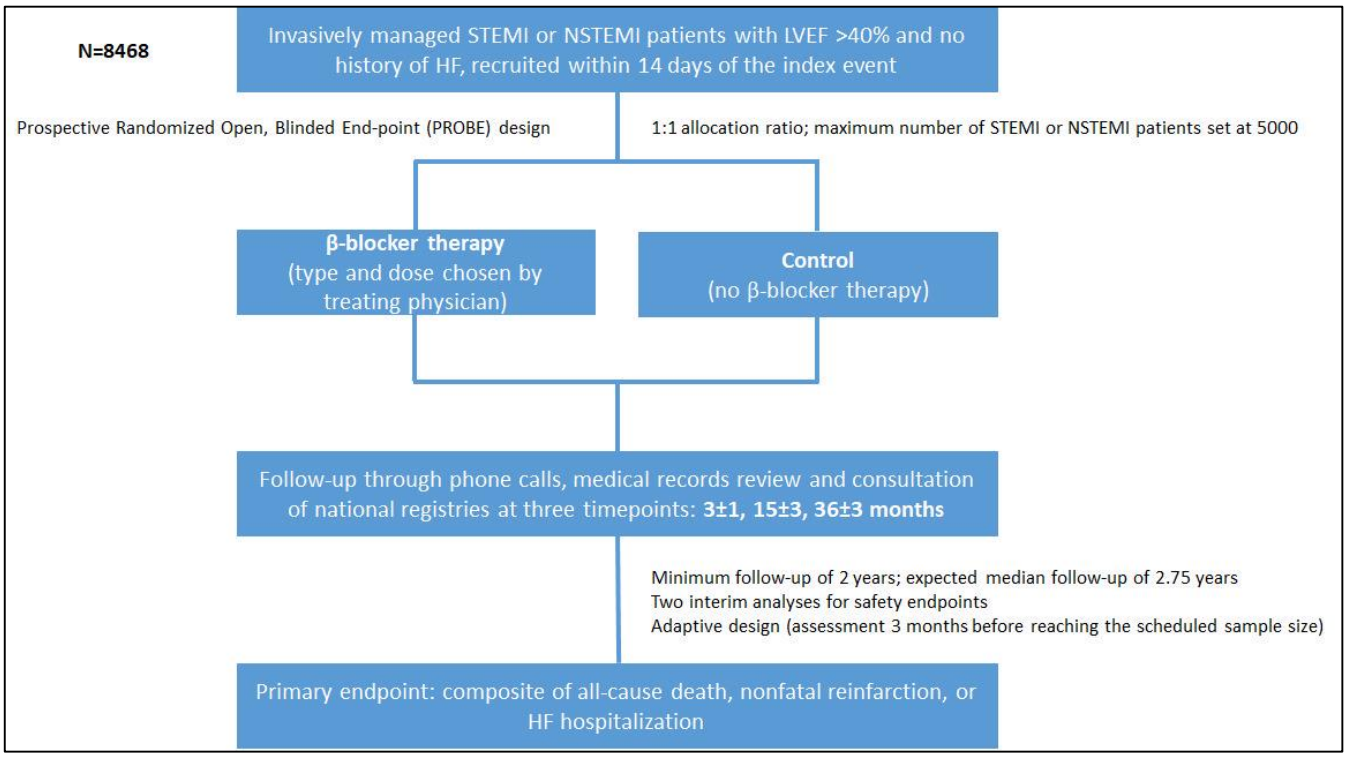
27. Dal-Re R, Avendano-Sola C, de Boer A, James SK, Rosendaal FR, Stephens R, Ioannidis JPA. A limited number of medicines pragmatic trials had potential for waived informed consent following the 2016 CIOMS ethical guidelines. J Clin Epidemiol 2019;**114**:60-71.

28. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;**362**(9377):7-13.

29. Rodriguez-Leor O, Cid-Alvarez B, Perez de Prado A, Rossello X, Ojeda S, Serrador A, Lopez-Palop R, Martin-Moreiras J, Rumoroso JR, Cequier A, Ibanez B, Cruz-Gonzalez I, Romaguera R, Moreno R, en representacion de los investigadores del Grupo de Trabajo sobre Codigo Infarto de la Asociacion de Cardiologia Intervencionista de la Sociedad Espanola de C, Villa M, Ruiz-Salmeron R, Molano F, Sanchez C, Munoz-Garcia E, Inigo L, Herrador J, Gomez-Menchero A, Gomez-Menchero A, Caballero J, Ojeda S, Cardenas M, Gheorghe L, Oneto J, Morales F, Valencia F, Ruiz JR, Diarte JA, Avanzas P, Rondan J, Peral V, Pernasetti LV, Hernandez J, Bosa F, Lorenzo PLM, Jimenez F, Hernandez JMT, Jimenez-Mazuecos J, Lozano F, Moreu J, Novo E, Robles J, Moreiras JM, Fernandez-Vazquez F, Amat-Santos IJ, Gomez-Hospital JA, Garcia-Picart J, Blanco BGD, Regueiro A, Carrillo-Suarez X, Tizon H, Mohandes M, Casanova J, Agudelo-Montanez V, Munoz JF, Franco J, Del Castillo R, Salinas P, Elizaga J, Sarnago F, Jimenez-Valero S, Rivero F, Oteo JF, Alegria-Barrero E, Sanchez-Recalde A, Ruiz V, Pinar E, Pinar E, Planas A, Ledesma BL, Berenguer A, Fernandez-Cisnal A, Aguar P, Pomar F, Jerez M, Torres F, Garcia R, Frutos A, Nodar JMR, Garcia K, Saez R, Torres A, Telleria M, Sadaba M, Minguez JRL, Merchan JCR, Portales J, Trillo R, Aldama G, Fernandez S, Santas M, Perez MPP. [Impact of COVID-19 on ST-segment elevation myocardial infarction care. The Spanish experience]. Rev Esp Cardiol 2020;**73**(12):994-1002.

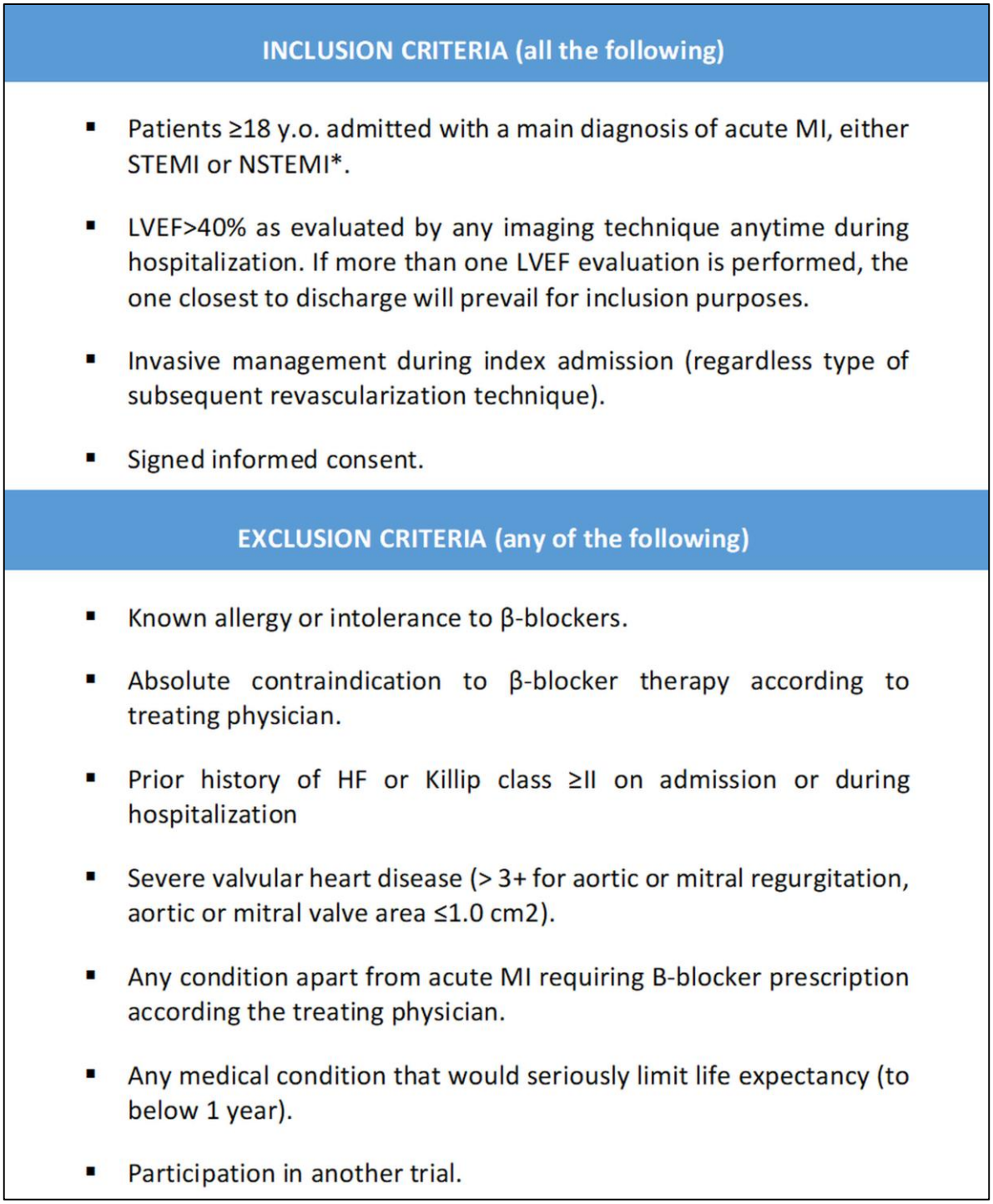
## Figure Legends

**Figure 1.** REBOOT study flowchart




*HF, heart failure*

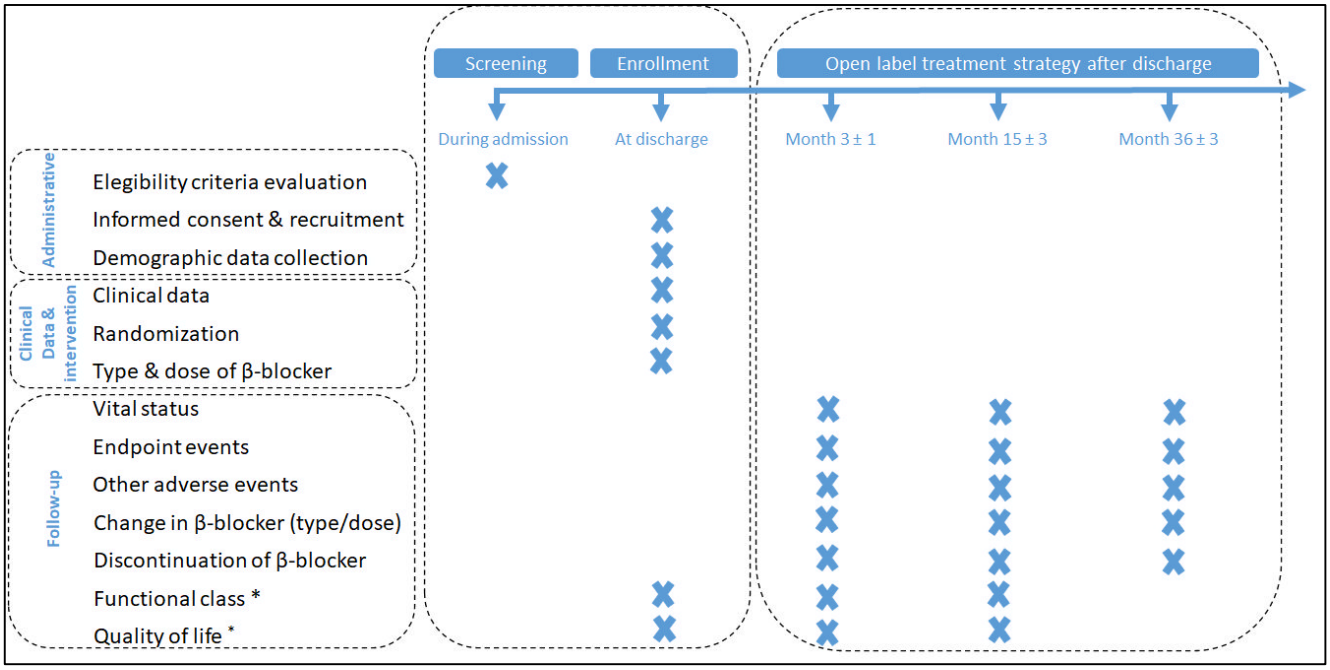
**Figure 2.** Enrollment criteria




*HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.*

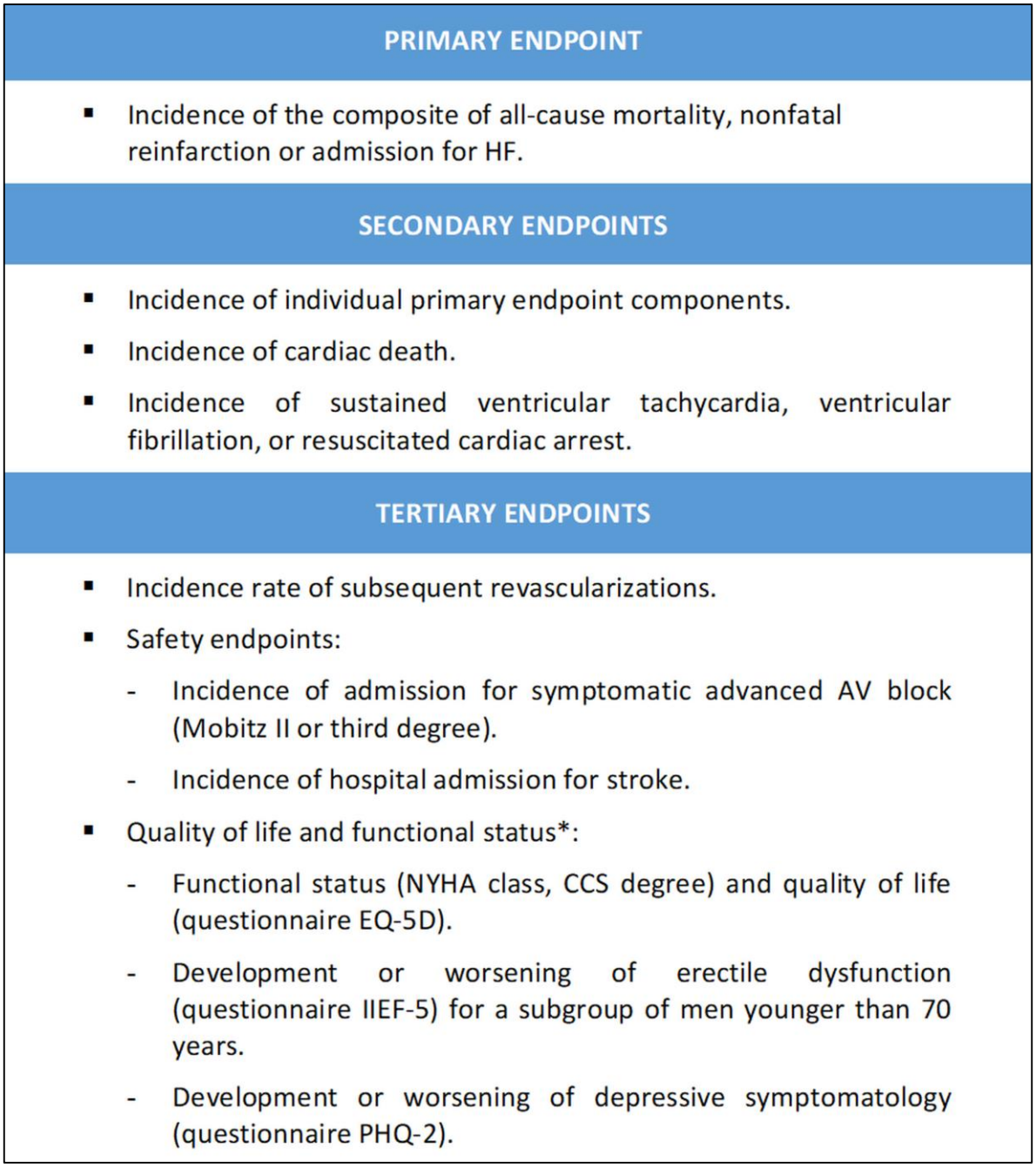
** The maximum number of STEMI or NSTEMI patients recruited is set at 5000. After recruitment of 5000 patients with one acute MI type, only patients with the other type will be recruited until the end of the study.*

**Figure 3.** Study data collection




* limited to a sub-sample of ≥1000 patients

**Figure 4. Study 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 ≥1000 patients

**Figure 5.** Pre-specified subgroups


*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.*

## APPENDIX

### ANNEX I. Full list of investigators/collaborators:

Abel Andres; Adriano Autieri; Albert Ariza; Alberto Cordero; Alessandra Costalunga; Alessandro Navazio; Alessandro Sionis; Alfonso Torres; Alfonso Valle; Alfredo Bardaji; Alfredo Renilla; Alina Olaru; Ana García-Alvarez; Ana Maria Campos; Angel Perez-Rivera; Annalisa Aloisi; Antonio Bayes-Genis; Antonio Ignacio Fernández Ortiz; Antonio Rizzo; Barbara Coutsoumbas; Beatrice Mariottoni; Camilla Renèe Zawaideh; Carlos Gonzalez-Juanatey; Carlos Tomás Querol; Carmen Rus; Claudio Vimercati; Danilo Saverio Vetrano; Delicia Gentille; Eduardo Alegría; Eduardo Arroyo; Eduardo Moreno Escobar; Efrén Martínez-Quintana; Elena Martinoli; Elvira Marco; Enrica Vitale; Enrico Nicolis; Erika Gazzola; Ezio Mesolella; Felipe Navarro; Francesco Manca; Francisco Fernández-Aviles; Francisco Marin-Ortuño; Francisco Torres; Gabriel Vázquez-Oliva; Gian Piero Perna; Gianni Casella; Giovanni Sirianni; Giuletta Grigis; Giulia Bugani; Giulia Pongetti; Giuseppe Di Tano; Gonzalo Navarrete; Hector Bueno; Hugo Paris; Ines Moeller; Isidro Hernandez; Ivana Pariggiano; J. Alberto San Román; Javier Botas; Jordi Palet; Jorge Sanchez; Jose A. Ramirez; José Angel Cabrera; José Díaz; José Manuel García Ruiz; Jose R Gonzalez-Juanatey; Jose Rozado; Josep Maria Alegret; Juan C García Rubira; Juan Luis Bonilla; Juan Ruiz-García; Juan Sanchis; Julio Hernandez; Lorenzo Calò; Mª Jesus Rollan; Manuel de Mora; Marco Solari; Maria Giulia Perrelli; Maria Rosa de Iacono; Mariachiara Buffa; Mario Lombardi; Matteo Bianco; Mauro Rondi; Natale Brunetti; Nicoletta De Cesare; Nicoletta De Santis; Oscar Diaz; Oscar Fabregat-Andres; Pablo Bazal; Pedro Morillas; Petra Sanz; Pierangelo Basso; Ricardo Ieva; Roberto Carletti; Roberto Martin; Roman Freixa; Rosa Fernandez; Rosario Ortas; Sabina Meloni; Stefano Tondi; Valentina Regazzoni; Vicente Mora; Agustín Martín García; Alba Cervero; Alba Martin; Albert Duran Cambra; Albert Massó- van Roessel; Alberto Pérez ; Alberto Pullara; Albina Aldomà; Alejandro Amador; Alejandro Junco; Alejandro Pascual; Alejandro Rodriguez; Alejandro Sanchez Grande-Flecha; Alejandro Villanueva; Alice Vitagliano; Alicia Bautista Pavés; Alicia Gainza; Alicia Moreno; Alvaro Aceña; Alvaro Vicedo; Ana Elvira Laffond; Ana Isabel Santos; Ana María Moralejo; Ana Merino; Ana M Pello-Lázaro; Ana Portoles; Ana Roman; Ana Testa; Ana Ayesta; Andrea Cafro; Andrea Chiampan; Andrea Finzi; Andrea Kallmeyer; Andrea Lopez; Andrea Rubboli; Andrea Veliz; Andrés Iñiguez; Andres Morist; Ane Aboitiz; Angel Franch; Angela Alonso; Angela Juez; Angelica Romero; Anna Carrasquer; Antonella Vasamì; Antoni Perelló-Bordoy; Antonia Sambola; Antonio Gamez; Antonio Jesus Martín; Antonio Lara-Padrón; Antonio Miñano; Antonio Piñero; Antonio Quesada; Antonio Tello; Aritz Gil; Armando Perez; Arturo Lanaspa; Aurora Diaz; Beatriz de Tapia Majado; Beatriz Saiz; Beatriz Samaniego; Beatriz Sampedro; Belen Alvarez; Belen Prado; Berenice Caneiro; Bernardo Ayala Borges ; Berta Vega; Betel Olaizola; Blanca Olivares; Carla Jimenez; Carlos Baladrón; Carlos Galán; Carlos Miguito; Carlos Millan Rodriguez; Carlos Ortiz; Carmen Guerrero; Carmen Palacios; Carolina Hernández-Luis; Carolina Redondo; Carolina Sorto; Cecilia Corros; Cecilia Lopez; Charo Cortina; Chiara Angeletti; Claudia Santos; Clea Gonzalez; Conchita Oliva; Cosme García; Cristina Cambeiro; Cristina Sanchez-Enrique; Cristina Tapia; Damaris de Sousa; Daniele Grosseto; Daniele Nassiacos; David Gomez; David Rutigliano; David Vivas; Deborah Cosmi; Diego Arroyo; Dolores Ruiz Fernández; Eduardo Caballero; Eduardo Zatarain; Elena Barbaresi; Elena Batlle; Elena España; Elena Lopez; Elena Tundidor; Elene Saez de Buruaga; Elisabeth Fernandez; Eliu David; Elizabet Méndez Eirín; Emad Abu Assi; Emanuela Clara Bertolino; Emilia Blanco; Enrico Cerrato; Enrico Gotti; Enrique Iglesias Río; Enrique Leon; Enrique Sanchez; Ernesto del Amo; Ernesto Hernandez; Esmeralda Capin; Ester Sánchez-Corral; Eugenio Vilei; Eva Gonzalez; Eva Santamaria; Eva Santamaria; Fabrizio Poletti; Federica del Giudice; Felice Achilli; Fernando Arribas; Filippo Maria di Dona; Flor Baeza; Francesca Pietrucci; Francisco José Pastor;

Francisco Manuel Burillo; Francisco Rivera; Fco Jesus Gonzalez; Gabriel Hurtado; Gabriel Sanchez; Gabriella Foresti; Gaspar Melis; Gerard Oristrell; Gian Battista Danzi; Giancarlo Piovaccari; Gianfranco Pistis; Gil Bonet; Giovanni Tortorella; Gislaine Castilho de Oliverira; Gonzalo Martin; Guillermo Moreno; Hector García; Hernan Tajes; Iciar García; Iciar Piedra; Idaira Famara Hernandez-Baldomero; Ignacio Sanchez; Inés García Lunar; Inmaculada Fernandez; Irene Buera; Irene Sempere; Irene Toribio; Iria Martinez; Iria Silva; Iris Garrido; Isabel Hernández; Itsaso Larrabide; Ivan Olavarri; Jairo Monedero; Jaume Pons; Javier Borrego; Javier Castrodeza; Javier López Díaz; Javier Maillo; Javier Mendoza; Javier Rekondo; Javier Simón; Javier Tobar; Javier Zueco; Jean Paul Vilchez Tschischke; Jessica Roa; Jessica Vaquero; Jessika Gonzalez; Jesus Carmona; Jesús Molina; Jesus Zarauza; José Ángel Rodríguez Fernández; Jose Enrique Romero; Jose Javier Sanchez; Jose Juan Jimenez; Jose Manuel Vazquez; Jose Miguel Rivera-Caravaca; Jose Seijas Amigo; Jose Tuñón; Josefa García; Juan Carlos Muñoz; Juan Escudero; Juan Franco; Juan Martínez Milla; Juan Ocampo Miguez; Julia Gonzalez; Julio Echarte; Laura Alvarez; Laura de la Fuente Blanco; Laura García; Laura Montagna; Laura Pertejo; Laura Rodríguez Sotelo; Leire Goikolea; Leire Goñi; Lidia Martinez; Lorena Garcia Riesco; Lucía Matute-Blanco; Lucía Pérez Cebey; Lucia Rioboo Leston; Luis Cerdán; Luis de la Fuente-Galán; Luis Martinez; Luis Ruiz Guerrero; Luna Carrillo; Luna Carrillo; Mª Asun Esteve; Magdalena Carrillo; Manel Sabate; Manuel Iglesias; Manuel Jesús Gómez; Manuel Lobo; Manuel Lopez; Marco Ruozzi; Marcos Farrais; Maria Alessandra Puteo; María del Carmen Gómez Rubín; Maria Facenda; Maria García; María Garrido; Maria Giovanna Pallotti; Maria Isabel Ezpeleta; Maria Jesus García; Maria Jose Antolinos; Maria Lasala; María López Alvarez; María López Benito; Maria Luisa Rodriguez; María Martín Mariscal; Maria Melendo; María Molina; Maria Ramos; Maria Rivadeneira; Maria Teresa Perez; Maria Vittoria Matassini; Mariam Quintanilla; Maribel Gonzalez; Marina Oliver; Marina Revilla; Marta Alonso-Fernández-de-Gatta; Marta Fernández; Marta Lopez; Marta Martin-Cabeza; Marta Monteagudo; Marta Santisteban; Marta Torres; Marta Torres; Massimo Piepoli; Matteo Azzarone; Matteo Lisi; Maurizio Mangiavacchi; Meryem Ezzitoun; Miguel AngelArnau Arnau; Miguel Lapeña; Miguel Molina; Miguel Puentes; Miguel Soroa; Mikel Martinez; Miquel Vives; Miriam Salim; Nacho Hernandez; Nadia Mollichelli; Nelva Sosa; Niccolò Simonelli; Nicola Locuratolo; Nieves Romero; Noelia Rojo-Prieto; Noemi Barja; Norberto Herrera Gómez; Nuria Sánchez; Olatz Zaldua; Onofre Caldes; Oriol De Diego; Oriol Rodriguez; Oscar González; Oscar M. Peiró; Oscar Vedia; Pablo Gil; Pablo Jorge-Pérez; Pablo Manuel Fernández; Pablo Jover-Pastor; Pablo Martinez; Pablo Pastor; Paloma Avila; Paolo Sganzerla; Pasquale Baratta; Pasquale Caldarola; Patricia Arenas; Pau Rello; Paula García; Paula Menendez; Pedro Luis Dorado; Pedro Martin; Pedro Vigil; Rafa Bourio; Rafael Cobas; Rafael Hidalgo; Rafael Moscicki; Ramon Andion; Ramon Rios; Raquel Díaz Muñoz; Raquel Marzoa; Raymundo Ocaranza; Roberto Martin; Rocío Barquero; Rocio Ruiz; Rodrigo Fernandez; Roi Bangueses; Romina Navarri; Rosa Agra; Rosa Sanchez; Ruben Bergel; Ruth Sanchez; Sandra Gómez Talavera; Santiago García-Mancebo; Sergio Cardenas; Sergio Huertas; Sergio Huertas; Silvia Bayona; Silvia Gopar; Silvia Lozado-Edo; Silvia Mera; Silvia Prieto; Silvia Stabellini; Simona D'Orazio; Sonia Santos; Susana Martinez Huertas; Tamara Fernández; Tamara García; Tania Seoane; Tania Seoane García; Teresa Simón; Toni Soriano; Ugo Limbruno; Valentina Pelizzoni; Valerio Epureanue; Vanesa Alonso; Verónica Artiaga; Vicente Bertomeu-Gonzalez; Vicente Peral; Víctor Donoso; Víctor Perez; Víctor Puebla Rojo; Victoria Espejo; Victoria Platero; Virginia Mass; Walter Bragagnini; Xurxo Martinez; Yolanda Gallego; Yvan Persia.

**ANNEX II. Full list of participating centers (alphabetical order):**

1. Alto del Guadalquivir;
2. Alvarez Buylla;
3. Arcispedale S. Maria Nuova, Reggio Emilia;
4. Arnau de Vilanova de Lleida;
5. Arquitecto Macide, Ferrol;
6. Basurto;
7. Bellvitge;
8. Bolognini, Seriate;
9. Burgos;
10. C.G.Morgagni, Forlì;
11. Cabueñes, Gijón;
12. Centro Nacional de Investigaciones Cardiovasculares (CNIC);
13. CHUAC Coruña;
14. CHUS, Santiago;
15. CHUVI Vigo;
16. Civile di Baggiovara;
17. Civile di Legnano;
18. Clinic Barcelona;
19. Clínico de Valencia;
20. Clínico de Valladolid;
21. Clinico San Carlos;
22. Complejo Universitario de Canarias;
23. Complejo Universitario Insular Materno Infantil;
24. Consorci Sanitari Integral;
25. Cremona;
26. Denia;
27. Desio;
28. Doce de Octubre;
29. Doctor Peset;
30. Fundación Alcorcón;
31. Fundación Althaia de Manresa;
32. Fundación Jimenez Díaz;
33. Galdakao Usansolo;
34. General de La Palma
35. General de Villalba;
36. General universitario de Elche;
37. General Universitario de Elda;
38. Germans Trias i Pujol;
39. Gran Canaria Doctor Negrín;
40. Gregorio Marañon;
41. Gualdo Tadino - Gubbio;
42. Guglielmo da Saliceto, Piacenza;
43. HUCA Oviedo;
44. IMED Valencia;
45. Infanta Elena Valdemoro;
46. Infermi di Rimini;

47. Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan;
48. Joan XXIII Tarragona;
49. Juan Ramón Jiménez, Huelva;
50. La Fe Valencia;
51. La Luz;
52. León;
53. Della Misericordia, Grosseto;
54. Lluis Alcanyis, Xativa;
55. Lucus Augusti, Lugo;
56. Maggiore di Bologna;
57. Marqués de Valdecilla, Santander;
58. Miguel Servet, Zaragoza;
59. Montecelo Pontevedra;
60. Navarra;
61. Nuestra Señora Candelaria;
62. Policlinico San Marco - Osio Sotto;
63. Presidio Ospedaliero di Passirana;
64. Presidio Ospedaliero di Saronno;
65. Quirón Pozuelo;
66. Regional Carlos Haya, Malaga;
67. Reina Sofía Córdoba;
68. Rey Juan Carlos Mostoles;
69. Río Hortega Valladolid;
70. Riuniti di Ancona;
71. Riuniti Foggia;
72. Ruber Internacional;
73. Ruber Juan Bravo;
74. Sacro Cuore Don Calabria, Negrar;
75. San Agustin, Aviles;
76. San Cecilio, Granada;
77. San Juan de Alicante;
78. San Juan de la Cruz, Ubeda;
79. San Luigi Gonzaga;
80. San Paolo di Bari;
81. Sant Joan de Reus;
82. Santa Creu i Sant Pau;
83. Santa Lucía Cartagena;
84. Santa Maria delle Croci, Ravenna;
85. Sant'Anna e San Sebastiano di Caserta;
86. Santi Antonio e Biagio di Alessandria;
87. Son Espases Mallorca;
88. Teknon;
89. Torrejón;
90. Torrevieja;
91. Treviglio;
92. Txagorritxu;
93. Universitario de Jaen;

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.