Beta-blockers after invasively managed STEMI vs NSTEMI without reduced ejection fraction: a pre-specified analysis from the REBOOT trial

Bloqueadores beta tras el tratamiento invasivo de STEMI frente a NSTEMI sin fracción de eyección reducida: un análisis preespecificado del ensayo REBOOT

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ABSTRACT

Introduction and objectives: Recent trials have questioned the clinical benefit of beta-blockers in post–myocardial infarction (MI) patients with preserved left ventricular ejection fraction (LVEF). However, differences in pathophysiology and risk profile between MI with and without ST-segment elevation myocardial infarction (STEMI and NSTEMI) may influence the effect of beta-blockers.

Methods: In this pre-specified subgroup analysis of the REBOOT trial, which randomized invasively managed MI patients with LVEF > 40% to beta-blockers or control, we evaluated differences in long-term effects of the intervention between STEMI (n = 4296) and NSTEMI (n = 4142). The primary endpoint was a composite of all-cause death, reinfarction, or heart failure hospitalization over a median follow-up of 3.7 years.

Results: The primary endpoint and components occurred more frequently in NSTEMI than STEMI. A significant interaction between MI type and beta-blocker allocation was observed (*P* = .027). Among STEMI patients, beta-blockers were associated with higher incidence of the primary endpoint (HR, 1.27, 95%CI, 1.00–1.62), whereas NSTEMI patients assigned to beta-blockers showed no effect (HR, 0.89, 95%CI, 0.72–1.10). Notably, NSTEMI patients with mildly-reduced LVEF (40% to 50%) on beta-blockers experienced significantly fewer events than controls.

Conclusions: The absence of clear clinical benefit from beta-blockers in invasively managed MI patients with preserved LVEF was consistent across STEMI and NSTEMI. The observed interaction by infarct type is exploratory and should not be interpreted as definitive evidence of harm associated with beta-blocker therapy in patients with STEMI and preserved LVEF. NSTEMI patients with mildly reduced LVEF may benefit from beta-blockers, warranting further investigations. (ClinicalTrials.gov: NCT03596385)

Keywords:

Beta-blockers; Acute coronary syndrome; STEMI; NSTEMI; Randomized controlled trial

RESUMEN

Introducción y objetivos: Ensayos recientes han cuestionado el beneficio clínico de los bloqueadores beta en pacientes tras infarto de miocardio (IAM) con fracción de eyección de ventrículo izquierdo (FEVI) conservada. Las diferencias en fisiopatología y perfil de riesgo entre IAM con y sin elevación del ST (IAMCEST e IAMSEST) podrían influir en su efecto

Métodos: En este análisis de subgrupos preespecificado del ensayo REBOOT, en el que se aleatorizó a pacientes con IAM tratados de forma invasiva y con una FEVI > 40% a recibir bloqueadores beta o tratamiento de control, se evaluó las diferencias en los efectos a largo plazo de la intervención entre los pacientes con IAMCEST (n = 4.296) y los pacientes con IAMSEST (n = 4.142). El objetivo principal primario fue un compuesto de muerte por cualquier causa, reinfarto u hospitalización por insuficiencia cardiaca durante un seguimiento mediano de 3,7 años.

Resultados: El objetivo principal y sus componentes ocurrieron más frecuentemente en IAMSEST que en IAMCEST. Se observó interacción significativa entre tipo de IAM y asignación a bloqueadores beta (p = 0,027). En IAMCEST, los bloqueadores beta se asociaron con mayor incidencia del objetivo principal (HR = 1,27; IC95%, 1,00–1,62), mientras que en IAMSEST no hubo diferencias (HR = 0,89; IC95%, 0,72–1,10). Pacientes con IAMSEST y FEVI intermedia (40–50%) tratados con bloqueadores beta presentaron significativamente menos eventos que los controles.

Conclusiones: La ausencia de beneficio de bloqueadores beta en IAM tratados invasivamente con FEVI conservada es consistente en IAMCEST e IAMSEST. La interacción observada por tipo de infarto es exploratoria y no debe interpretarse como una señal definitiva de daño asociado a uso de bloqueadores beta en IAMCEST. Pacientes con IAMSEST y FEVI parecen beneficiarse de bloqueadores beta, requiriendo investigación adicional en estudios adecuados. (ClinicalTrials.gov: NCT03596385)

Palabras clave: Bloqueadores beta; Síndrome coronario agudo; IAMCEST; IAMSEST; Ensayo clínico aleatorizado

Abbreviations

HF: heart failure

LVEF: left ventricular ejection fraction

MI: myocardial infarction

NSTEMI: non-ST-segment elevation myocardial infarction

STEMI: ST-segment elevation myocardial infarction

Abreviaturas

FEVI: fracción de eyección del ventrículo izquierdo

IAM: infarto agudo de miocardio

IAMCEST: infarto agudo de miocardio con elevación del segmento ST

IAMSEST: infarto agudo de miocardio sin elevación del segmento ST

VI: ventrículo izquierdo

INTRODUCTION

Despite the widespread use of contemporary medical therapies, a significant residual risk of adverse cardiovascular outcomes persists following acute myocardial infarction (MI).[1,2] Beta-blockers have historically been a cornerstone in the management of MI.[3] In patients with left ventricular ejection fraction (LVEF) ≤ 40%, including those after a MI, the benefits of beta-blockers in reducing mortality are well established.[4,5] In contrast, the benefit of beta-blockers in post-MI patients without reduced LVEF (> 40%) remained largely unexplored until recently. Current recommendations for this group are largely based on older clinical trials conducted in an era where timely reperfusion, complete revascularization, high-sensitivity troponin assays, potent dual antiplatelet therapy and high intensity statins were not in place.[6] Nevertheless, both American and European guidelines continue to recommend beta-blockers for post-MI patients without reduced LVEF (Class I-A in American guidelines; Class IIa-B in European guidelines).[7-9]

However, this dogma has been recently challenged by several pragmatic randomized clinical trials testing the benefits of beta-blockers in this population. Four contemporary pragmatic trials have tested the benefit of beta-blockers in post-MI patients treated according to current standards. Three of them showed no benefit of beta-blockers[10-12] and a fourth one (BETAMI-DANBLOCK trials, jointly reported) suggested a reduction in reinfarction rate associated with beta-blockers.[13] Two recent individual-patient meta-analyses of these have confirmed that, while in patients with mildly reduced LVEF, beta-blockers seem to offer a benefit,[14] patients with preserved LVEF do not benefit from beta-blocker therapy.[15] These results are in line with the REBOOT trial.

The old trials that founded the long-standing recommendation for beta-blockers after MI were mostly performed in ST-segment elevation myocardial infarction (STEMI) populations.[5,16] From a pathophysiological perspective, STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) differ substantially in their impact on left ventricular structure and composition, including the extent and transmurality of myocardial necrosis. STEMI is typically associated with a larger infarct size and greater

scar burden due to complete and sustained coronary artery occlusion, whereas NSTEMI often results from partial or transient occlusion, leading to smaller, subendocardial damage. These differences translate into distinct risks of malignant ventricular arrhythmias and heart failure (HF) risk, features classically associated with higher mortality risk. As beta-blockers exert their clinical benefit through anti-arrhythmic, anti-ischemic, HF prevention, and negative inotropic effects, their therapeutic impact may not be uniform across MI subtypes (STEMI and NSTEMI).

Here, we present the results of a pre-specified subgroup analysis from the REBOOT trial, evaluating the long-term benefits of beta-blocker therapy according to the type of acute MI (STEMI vs NSTEMI).

METHODS

Study population

The tREatment with beta-blockers after myOcardial infarction without reduced ejection fraction (REBOOT) trial (ClinicalTrials.gov identifier: NCT03596385; European Clinical Trials Database number: 2017-002485-40) was an independent, investigator-initiated study whose design has been previously described.[17] Briefly, REBOOT was a pragmatic, multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial conducted in Spain and Italy.

Eligible patients met the following main inclusion criteria: a) STEMI or NSTEMI with invasive management during the index hospitalization (ie, coronary angiography); and b) LVEF > 40% prior to discharge, assessed by any imaging modality. Key exclusion criteria included: a) a history of HF or the presence of Killip class ≥ II at any point during the index event; and b) any absolute contraindication to beta-blocker therapy or any condition (apart from acute MI) that requires beta-blocker prescription on discharge (both according to the treating physician).

Patients meeting all criteria were randomized at discharge or within 14 days (mean 3.8 ± 2.6 days from index MI) to receive either beta-blocker therapy (intervention group) or no beta-blocker therapy (control group). In the intervention group, the type and dose of beta-blocker were determined by the managing physician. Apart from beta-blockers, all patients received standard-of-care treatment at the discretion of the treating physician.

All participants provided written informed consent before enrollment. The study protocol was approved by the relevant ethics committees in Spain (EC79-17/FJD) and Italy (Reg. sperimentazioni n.2085, Prot. 9144/2018; I.5/109).

After exclusions, 8438 (out of the 8505 enrolled population) were included in the intention-to-treat analysis and are included in the present study.

Clinical outcomes

The primary outcome of the REBOOT trial was a composite of all-cause mortality, non-fatal reinfarction, or HF admission. Secondary outcomes included individual components of primary endpoint (all-cause mortality, non-fatal reinfarction, and HF admission), cardiac death, and malignant ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, or resuscitated cardiac arrest). Admission for stroke was a key tertiary safety endpoint.

Follow-up assessments of clinical outcomes were conducted at 3, 15, 36, and 48 months after randomization, through telephone interviews and review of medical records and national vital status registries. Events were centrally adjudicated by a panel blinded to the study treatment assignment.

Statistical analysis

A pre-specified subgroup analysis by type of MI was pre-defined in the study protocol. Main analyses were performed according to the intention-to-treat principle using proportional hazard models to generate unadjusted hazard ratios and 95% confidence intervals (95%CI) stratified by type of MI (STEMI or NSTEMI) with a likelihood ratio test for interaction. Kaplan-Meier curves were used to plot the cumulative incidence of the primary outcome and its components by treatment group within each MI type. An additional per-protocol analysis was performed, with patient follow-up censored at the point of known crossover (ie, beta-blocker patient stopped taking it or non-beta-blocker patient started taking it). Results are presented without formal adjustment for multiplicity. Subgroup analyses were performed for the primary endpoint for pre-defined baseline characteristics, with HRs and 95%CIs displayed for each subgroup category in a forest plot. All analyses were performed using STATA version 18.5 (StataCorp).

RESULTS

Baseline characteristics

Among the 8438 patients included in the intention-to-treat population, 4296 had STEMI (2146 assigned to beta-blocker and 2150 to no beta-blocker), and 4142 had NSTEMI (2061 and 2081 assigned to beta-blocker and no beta-blocker, respectively).

Baseline characteristics and in-hospital management details according to MI type and treatment allocation are provided in table 1 and table S1. Compared with patients with STEMI, those presenting with NSTEMI were older, more frequently female, and had a higher prevalence of hypertension, diabetes, dyslipidemia, and prior MI or stroke. In contrast, current smoking was more prevalent among STEMI patients. Baseline characteristics were well balanced across treatment groups within each MI type.

Discharge medications are shown in table 2. In both STEMI and NSTEMI groups, the use of dual antiplatelet therapy and statins was very high (> 98%). Prescription rates of ACE inhibitors (ACEi) or angiotensin

receptor blockers (ARBs) were also high (~75%) and similar between MI types. ACEi/ARB, ivabradine and calcium channel blockers were more frequently prescribed in the no beta-blocker group, in both STEMI and NSTEMI populations. Among patients allocated to the beta-blocker group, bisoprolol was the most commonly prescribed agent, regardless of MI type.

Clinical outcomes

Table 3 shows the event rates according to treatment allocation and type of MI. Over a median follow-up of 3.7 years, the incidence of the primary endpoint and its components were higher in NSTEMI than in the STEMI populations. Similarly, the rate of cardiac death and stroke were higher in the NSTEMI than in the STEMI population. The rate of malignant arrhythmias was very low and not different between type of MI.

A significant interaction (P = .027) was found between type of MI and treatment allocation for the incidence of the primary outcome (death, reinfarction of HF admission). In the STEMI population, the primary composite outcome occurred in 149 (20.8/1000 person-years) and 119 (16.3/1000 person-years) in beta-blocker and no beta-blocker groups respectively (HR, 1.27; 95%CI, 1.00-1.62). In NSTEMI population, the primary composite outcome occurred in 167 (24.3/1000 person-years) and 188 (27.4/1000 person-years) in beta-blocker and no beta-blocker groups respectively (HR, 0.89; 95%CI, 0.72-1.10). Figure 1 shows the Kaplan-Meier curves for the primary outcome in STEMI and NSTEMI populations. The rate of secondary outcomes and tertiary safety endpoint were numerically higher in patients in the beta-blocker group in the STEMI population and lower in the beta-blocker group in the NSTEMI population. However, no significant interactions were found for these endpoints. Figure 2 shows the Kaplan-Meier curves for the components of the primary outcome. The total number of events are shown in table S2. In the per-protocol analysis, consistent findings were obtained with significant interaction between type of MI and treatment allocation both for the primary outcome and for all cause death events (table S3). In STEMI patients, the

effect of beta-blocker on the primary endpoint was consistent across all pre-specified subgroups (figure 3). However, in NSTEMI patients, a significant interaction was observed between LVEF and treatment allocation (figure 4): NSTEMI patients with mildly reduced LVEF (40% to 49%) allocated to beta-blocker group had significantly less rate of the primary composite outcome than those allocated to no beta-blockers (HR, 0.46, 95%CI, 0.23-0.90). This beneficial effect of beta-blockers was not observed for NSTEMI patients with preserved LVEF.

Admission for stroke (safety tertiary endpoint) was not different between STEMI patients allocated to beta-blocker or no beta-blocker. However, in the NSTEMI population, the rate for stroke was higher in patients allocated to beta-blockers (HR, 2.43; 95%CI, 1.16-5.08). *P* value for interaction between type of MI and treatment allocation for the incidence rate of stroke was .053 (table 3).

DISCUSSION

In this prespecified subgroup analysis of the REBOOT trial, we evaluated the impact of beta-blocker therapy on the primary composite outcome (all-cause death, myocardial reinfarction, or HF hospitalization), as well as on secondary and safety endpoints, according to the type of MI (STEMI or NSTEMI). The main findings are as follows: a) NSTEMI patients represented a higher-risk population compared to those with STEMI, being older and having a higher prevalence of cardiovascular risk factors; b) In line with their baseline risk, the incidence of all clinical endpoints during follow-up was higher in the NSTEMI group than in the STEMI group; c) Overall prescription rates of secondary prevention therapies were high across all groups, with > 98% of patients discharged on DAPT and statins. Patients in the beta-blocker group were less frequently prescribed ACEi/ARBs compared to those in the no beta-blocker group (73% vs 78% in STEMI, and 72% vs 77% in NSTEMI); d) A significant interaction was observed between MI type and treatment allocation for the primary composite outcome: beta-blocker use was associated with

a numerically higher event rate in STEMI patients, but a numerically lower event rate in NSTEMI patients, compared to those not receiving beta-blockers. This pattern was consistent across all individual components of the composite endpoint and in cardiac death; and d) NSTEMI patients with midrange LVEF (41% to 50%) allocated to beta-blockers appeared to have a significant reduction in the incidence rate of the primary composite outcome. Figure 5 summarized these results.

The most robust conclusion of this analysis is that the absence of clinical benefit from beta-blocker therapy after MI was consistent across both STEMI and NSTEMI populations. This conclusion is in line with a recent meta-analysis including 18 000 patients.[15] The unexpected increase in event rates among STEMI patients treated with beta-blockers in REBOOT warrants further investigation since the possibility of type I error cannot be ruled out. This study is not the first to suggest that, in STEMI patients treated according to current standards—including timely reperfusion, complete revascularization, and contemporary secondary prevention pharmacotherapy—beta-blocker therapy may be associated with higher event rates. In an observational study of 3692 STEMI patients, the adjusted incidence of cardiac death or reinfarction was significantly higher among those receiving beta-blockers.[18] Similarly, in a large registry-based analysis, STEMI patients showed a non-significant trend favoring no beta-blocker therapy, whereas the opposite pattern was observed in NSTEMI patients.[19] In a recent meta-analysis pooling data from observational studies and trials performed after 2010 showed that STEMI patients with preserved LVEF had a (non-significant) higher event rate when on beta-blockers.[20]

Regarding the possible benefit of beta-blockers in NSTEMI patients with midrange LVEF (41% to 50%), the interpretation of this observed finding requires caution. The sample size in this subgroup was relatively small (165 patients allocated to beta-blockers and 142 to no beta-blockers), which increases the likelihood of random variation and limits the robustness of the effect estimate (HR, 0.46; 95%CI, 0.23–0.90). Importantly, a similar signal of potential benefit in patients with LVEF 40% to 50% was previously reported

in the meta-analysis by Rosselló et al.,[14] suggesting that this subset may represent a physiologically distinct group, possibly more sensitive to the anti-ischemic and anti-remodeling effects of beta-blockade.

The current management of patients with acute MI has evolved substantially compared to 4 decades ago, when the first beta-blocker trials were conducted. This applies both to the in-hospital management and to the long-term secondary prevention pharmacotherapy. At the time of the old beta-blocker trials, MI patients experienced markedly higher event rates, with annual mortality and reinfarction rates exceeding 5% for each outcome.[21-23] In contrast, contemporary trials and cohort studies rates are nearly threefold lower. As an example, in the REBOOT trial in MI patients without reduced LVEF, the annual mortality rate was around 1.1%, almost identical to that reported in the in REDUCE-AMI trial.[24] Given this evolving landscape, it is essential to re-evaluate the clinical benefit of therapies whose efficacy was established in an era when the standard of care differed markedly from current practice. This is particularly relevant for beta-blockers, as their historical clinical benefit was primarily attributed to the prevention of malignant arrhythmias, attenuation of adverse left ventricular remodeling, and preventing reinfarction in patients with residual severe coronary artery disease—mechanisms that are far less prevalent in the contemporary era of early reperfusion, complete revascularization, and optimized medical therapy. A recent meta-analysis reported that beta-blockers reduced cardiovascular events in the pre-reperfusion era, but not in the reperfusion era.[25] This is not the case for MI patients with severe left ventricular dysfunction, where beta-blockers still confer benefits, improving left ventricular remodeling and playing a role in myocardial protection.[4]

In addition, the ABYSS trial evaluated whether discontinuation of long-term beta-blocker therapy after MI was non-inferior to continuation.[26] The study enrolled patients who had remained clinically stable for a median of 2.9 years following their infarction and randomized them to either continue or discontinue beta-blocker treatment. Discontinuation of beta-blockers did not result in any difference in hard clinical outcomes, including death, reinfarction, or hospitalization for HF. However, an increase in hospitalizations

for cardiovascular causes not related to these hard endpoints was observed in the discontinuation group. Given the open-label design of the trial and considering that no differences were observed in major adverse cardiovascular outcomes, the findings of ABYSS appear to be consistent with those of REBOOT and other contemporary trials, which collectively suggest that beta-blocker therapy after MI is not associated with any meaningful clinical benefit in patients with preserved LVEF.

Classically, STEMI patients were considered the highest-risk subgroup within the spectrum of acute coronary syndromes, primarily due to the extent of myocardial necrosis resulting from prolonged coronary occlusion.[27,28] However, the widespread adoption of early reperfusion and invasive strategies has fundamentally altered the pathophysiological substrate, such that STEMI patients no longer represent the population with the highest long-term cardiovascular risk.[29,30] Indeed, as also observed in the present study, STEMI presentation is now more frequently seen in younger patients with fewer comorbidities. Conversely, NSTEMI presentation is typically seen in older patients at higher burden of cardiovascular risk factors and comorbid conditions, translating into a worse long-term prognosis compared with their STEMI counterparts. Given this more favorable cardiovascular risk profile, STEMI patients may derive less benefit from therapies such as beta-blockers. However, the observed signal for harm in STEMI patients allocated to beta-blocker therapy in the REBOOT trial should be interpreted with caution. Although similar findings have been reported in other observational studies,[19,20,28] they are not consistent across the literature.

The apparent opposite pattern observed in response to beta-blockers between STEMI and NSTEMI patients can be explained, at least in part, by baseline risk profile and comorbidities. NSTEMI patients are generally older and have a higher burden of cardiovascular risk factors and comorbidities, making them more susceptible to the beneficial effects of beta-blockers, including heart rate reduction, prevention of recurrent ischemic events, and hemodynamic control. In contrast, contemporary STEMI patients tend to be younger and have fewer comorbidities and may derive less benefit from beta-blocker therapy in the absence of significant ventricular dysfunction.

The underlying mechanisms potentially linking beta-blocker used to increased adverse events in STEMI patients remain speculative. In the REBOOT trial, beta-blocker-treated patients were less frequently prescribed ACEi/ARBs. This finding may reflect clinical practice patterns, as the REBOOT trial had a pragmatic design, leaving treatment decisions to the discretion of attending physicians. A similar pattern was observed in REDUCE-AMI,[24] where ACEi use was slightly lower in the beta-blocker group compared to controls (79% vs 81%). This different prescription rate of ACEi/ARBs in patients in the control arm was also observed in the BETAMI-DANBLOCK trials (41% vs 45%).[13] Of note, ACEi/ARB prescription rates in the REBOOT trial was higher than those reported in observational cohorts. The difference in ACEi/ARBs prescription between treatment groups was more pronounced in REBOOT (72% vs 77%) than in REDUCE-AMI.[24] or BETAMI-DANBLOCK.[13] As ACEi have demonstrated clear benefits in MI patients—particularly in those with STEMI[31,32]—it is plausible that differences in ACEi/ARB use may have contributed, at least in part, to the higher event rates observed among beta-blocker–treated STEMI patients.

In the REBOOT trial, NSTEMI patients exhibited a substantially worse cardiovascular risk profile and experienced markedly higher event rates than those with STEMI. In those NSTEMI patients —who are older and have a higher cardiovascular risk than STEMI patients— beta-blockers could be associated with a higher risk of stroke, as we observed in the present trial, consistent with what has been previously described.[33] Our findings should be considered exploratory and hypothesis-generating, given the low absolute number of strokes and the absence of a statistically significant interaction. Nonetheless, there are plausible pathophysiological explanations. Beta-blockers have been shown to be less effective than renin angiotensin system inhibitors or calcium channel blockers in stroke prevention, particularly in hypertensive patients, and their effect on central blood pressure reduction and arterial stiffness is inferior to that of other drug classes. In this context, higher use of beta-blockers may have partially displaced the prescription or intensification of other agents with greater proven efficacy in stroke prevention, such as ACE inhibitors/ARBs or calcium channel blockers, as observed in our study with a lower rate of ACE

inhibitor/ARB use in the beta-blocker-treated group. Post hoc analyses of the STEP trial and other studies in older populations have suggested an increased risk of cardiovascular events—including stroke—associated with beta-blocker–based strategies, which may be especially relevant in a population like NSTEMI patients, characterized by advanced age and higher comorbidity burden.[34] Furthermore, in the POISE trial (enrolling patients undergoing non cardiac surgery), randomization to betablockers was associated with a higher incidence of ischemic strokes during follow-up.[35] Despite the use of invasive strategies, complete revascularization, and high prescription rates of dual antiplatelet therapy and statins, NSTEMI patients remain at increased risk for long-term adverse outcomes, including all-cause and cardiovascular mortality. These findings highlight the need for future research specifically aimed at improving outcomes in the high-risk NTEMI population.

Limitations

The present study has several limitations. First, although this subgroup analysis was prespecified in the trial protocol, all subgroup analyses carry inherent risks of bias and should be interpreted as hypothesis-generating due to the lack of adjustment for multiple testing.[36] Dedicated prospective trials in the respective subgroups are needed to confirm these findings definitively. Second, REBOOT was an open-label trial, as blinding was deemed unfeasible due to its pragmatic design. While neither patients nor treating physicians were blinded to treatment allocation, clinical endpoints were adjudicated by a central committee blinded to group assignment. The lower rate of ACEi/ARB prescription in the beta-blocker group may have been influenced by knowledge of treatment allocation by clinicians, potentially contributing to the observed signal of harm in the STEMI subgroup. However, this limitation does not invalidate the consistent lack of benefit observed with beta-blocker therapy across both MI types. Third, the trial experienced a moderate rate of treatment crossover or discontinuation. At 15 months, 12.9% of patients assigned to the beta-blocker group had discontinued treatment, whereas 17.6% of patients in the

no–beta-blocker group had initiated beta-blocker therapy.[10] Nevertheless, per-protocol analyses yielded results consistent with those of the intention-to-treat analysis, supporting the robustness of the findings. Fourth, given that bisoprolol was the predominantly used beta-blocker, it remains unclear whether the observed effects can be generalized to all beta-blockers as a class or whether important differences may exist between individual agents. However, in the recent meta-analysis published no interaction by beta-blocker type was observed, suggesting that the effect is likely to represent a class effect.[15] Fifth, another limitation of this study is the low proportion of women included (about 20% in the NSTEMI cohort), which is lower than observed in real-world populations. Finally, the trial was conducted exclusively in Spain and Italy, countries characterized by relatively lower baseline cardiovascular risk[37] and predominantly Caucasian populations, which may limit the generalizability of the results to other geographic and ethnic populations.

CONCLUSIONS

This prespecified subgroup analysis of the REBOOT trial demonstrates that the absence of clinical benefit from beta-blocker therapy in invasively managed MI patients with preserved LVEF (> 40%) is consistent across both STEMI and NSTEMI populations. STEMI patients, who carry a lower long-term cardiovascular risk than NSTEMI, experienced a higher incidence of adverse events when treated with beta-blockers. In contrast, NSTEMI patients with midrange LVEF (40% to 50%) emerged as a subgroup that may derive clinical benefit from beta-blocker therapy. Although a differential interaction by infarct type was observed, these exploratory results cannot support firm conclusions regarding potential harm in STEMI or benefit in NSTEMI. Instead, they should be viewed as hypothesis-generating observations that warrant further investigation in ad hoc studies.

FUNDING

REBOOT-CNIC was an independent trial funded by the Centro Nacional de Investigaciones Cardiovasculares (CNIC). The CNIC is supported by the Instituto de Salud Carlos III (ISCIII), the Ministerio de Ciencia, Innovación y Universidades and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIU/AEI/10.13039/501100011033).

ETHICAL CONSIDERATIONS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. The study protocol was approved by the relevant ethics committees in Spain (EC79-17/FJD) and Italy (Reg. sperimentazioni n.2085, Prot. 9144/2018; I.5/109). All participants provided written informed consent before enrollment. The privacy rights of all subjects were strictly observed, and no identifiable patient information is included in this article. The SAGER guidelines have been followed with respect to possible sex/gender bias.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in the preparation of this manuscript. The authors take full responsibility for the content of the publication.

AUTHORS' CONTRIBUTIONS

S. Raposeiras-Roubín and M. Anguita equal contribution as first authors. S. Raposeiras-Roubín: realizó el primer borrador del manuscrito y contribuyó a los análisis de los datos. M. Anguita: contribuyó a la

realización de la investigación y efectuó una revisión crítica del manuscrito enviado. R. Latini: contribuyó a la supervisión del estudio y aprobó la versión final del manuscrito. A. Domínguez-Rodríguez: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. J.A. Barrabés: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. P.L. Sánchez: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. F. Ottani: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. S. Pocock: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. R. Owen: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. P. Cristobo: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. S. Gómez-Talavera: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. L. Staszewsky: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. N. Escalera: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. F. Fernández-Vazquez: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. M. Bianco: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. Ó. Prada-Delgado: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. C. Nicolás Pérez-García: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. V. Pelizzoni: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. F. Navarro: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. J.-Á. Perez-Rivera: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. G. Martín-Gorria: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. A. Vetrano: contribuyó a la realización de la investigación y efectuó una revisión crítica del manuscrito enviado. V. Fuster: contribuyó a la evaluación crítica del manuscrito y aprobó la versión final. X. Rosselló: realizó el primer

borrador del manuscrito y contribuyó a los análisis de los datos. B. Ibáñez: concibió el estudio, supervisó su desarrollo y otorgó la aprobación final del manuscrito enviado. B. Ibáñez y X. Rosselló contribuyeron por igual como autores de correspondencia y comparten la responsabilidad de la correspondencia relacionada con este manuscrito.

CONFLICTS OF INTEREST

Nothing to disclose.

WHAT IS KNOWN ABOUT THE TOPIC?

Beta-blockers have long been recommended after myocardial infarction, but their benefit in patients without reduced LVEF has been increasingly questioned in the contemporary reperfusion era. Recent randomized trials and meta-analyses have shown no clear overall benefit in post-MI patients with preserved LVEF, while a possible benefit may persist in those with mildly reduced LVEF. Because STEMI and NSTEMI differ in pathophysiology, infarct characteristics, and baseline risk, the effect of beta-blockers may not be uniform across MI subtypes.

WHAT DOES THIS STUDY ADD?

This prespecified REBOOT analysis shows that, in invasively managed MI patients with LVEF >40%, the absence of clear beta-blocker benefit was consistent in both STEMI and NSTEMI overall. It also identified a significant interaction by infarct type: beta-blockers were associated with a higher rate of the primary composite outcome in STEMI, whereas no overall effect was observed in NSTEMI. Importantly, NSTEMI

patients with mildly reduced LVEF (40%–49%) appeared to benefit from beta-blockers, supporting the need for more tailored post-MI treatment strategies.

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Table 1

Baseline characteristics according to type of infarction and treatment allocation

Characteristics	**STEMI**		**NSTEMI**	
	Beta-blocker	**No beta-blocker**	**Beta-blocker**	**No beta-blocker**
	(N = 2146)	**(N = 2150)**	**(N = 2061)**	**(N = 2081)**
Demographics				
Age (years)	59.9 ± 10.9	60.0 ± 10.7	62.8 ± 11.3	62.7± 11.3
Sex				
Male	1749 (81.5)	1780 (82.8)	1642 (79.7)	1640 (78.8)
Female	397 (18.5)	370 (17.2)	419 (20.3)	441 (21.2)
Medical history				
Arterial hypertension	996 (46.5)	983 (45.9)	1186 (57.7)	1202 (58.0)
Diabetes mellitus	392 (18.3)	401 (18.8)	509 (24.8)	492 (23.8)
Dyslipidemia	1058 (49.4)	1049 (49.0)	1100 (53.5)	1117 (53.9)
Smoker	1083 (51.8)	1090 (52.2)	768 (38.3)	734 (36.2)
Prior MI	131 (6.1)	133 (6.2)	277 (13.5)	261 (12.6)

Prior stroke	27 (1.3)	26 (1.2)	59 (2.9)	41 (2.0)
Atrial fibrillation prior to admission	26 (1.2)	38 (1.8)	65 (3.2)	64 (3.1)
Peripheral arterial disease	45 (2.1)	40 (1.9)	82 (4.0)	72 (3.5)
History of COPD	57 (2.7)	60 (2.8)	88 (4.3)	73 (3.5)
Treatment with beta-blockers before index admission	183 (8.5)	200 (9.4)	327 (16.0)	309 (14.9)
Echocardiographic and angiographic data				
LVEF (%)	56.0 ± 7.2	56.1 ± 7.1	58.0 ± 6.9	58.4 ± 7.0
Infarct related artery				
None	15 (0.7)	11 (0.5)	86 (4.2)	101 (4.9)
Left anterior descending	527 (24.6)	531 (24.8)	608 (29.6)	608 (29.3)
Left circumflex system	233 (10.9)	254 (11.9)	299 (14.6)	240 (11.6)
Right coronary artery	739 (34.5)	749 (35.0)	344 (16.8)	367 (17.7)
Secondary	122 (5.7)	81 (3.8)	118 (5.7)	139 (6.7)
Left main	11 (0.5)	9 (0.4)	19 (0.9)	21 (1.0)
Multivessel	494 (23.1)	508 (23.7)	579 (28.2)	596 (28.8)
Type of revascularization				

None	47 (2.2)	33 (1.5)	160 (7.8)	157 (7.6)
PCI	2061 (96.0)	2073 (96.4)	1845 (89.5)	1852 (89.0)
Complete revascularization	1815 (89.2)	1817 (89.1)	1649 (86.8)	1667 (87.7)

AF, atrial fibrillation; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; LDL, low-density lipoprotein; 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; SBP, systolic blood pressure; WBC, white blood cell.

Data are expressed as no. (%), mean ± standard deviation or median [interquartile range].

Table 2

Discharge medication

Pharmacological agent	**STEMI**		**NSTEMI**	
	Beta-blocker	**No beta-blocker**	**Beta-blocker**	**No beta-blocker**
	(N = 2146)	**(N = 2150)**	**(N = 2061)**	**(N = 2081)**
Aspirin	2124 (99.2)	2125 (99.0)	2012 (97.7)	2040 (98.1)
$P2Y_{12}$ inhibitors	2128 (99.3)	2129 (99.2)	1992 (96.7)	2000 (96.2)
Oral anticoagulants	71 (3.3)	75 (3.5)	99 (4.8)	89 (4.3)
Beta-blockers	2117 (98.7)	81 (3.8)	2010 (97.6)	128 (6.2)
Type of beta-blocker				
Atenolol	9 (0.4)		17 (0.8)	
Bisoprolol	1850 (87.4)		1699 (84.4)	
Carvedilol	62 (2.9)		66 (3.3)	
Metoprolol	146 (6.9)		163 (8.1)	
Nebivolol	49 (2.3)		65 (3.2)	
Other	1 (0.0)		4 (0.2)	

ACE-i/ARB	1567 (73.3)	1675 (78.1)	1473 (71.7)	1594 (76.7)
Statins	2114 (98.7)	2127 (99.1)	2016 (97.9)	2034 (97.9)
Aldosterone receptor antagonist	50 (2.3)	46 (2.1)	43 (2.1)	38 (1.8)
Ivabradine	8 (0.4)	133 (6.2)	12 (0.6)	110 (5.3)
Calcium channel blockers	140 (6.6)	159 (7.4)	291 (14.1)	356 (17.2)

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Data is summarized as frequency (%).

Table 3

Analysis of primary, secondary and tertiary endpoints

Endpoint	**STEMI**				**NSTEMI**				***P* value**
	N (rate per 1000 person-years)		**Rate difference (95%CI)**	**HR (95%CI)**	**N (rate per 1000 person-years)**		**Rate difference (95%CI)**	**HR (95%CI)**	***P* for interaction**
	Beta-blocker	**No beta-blocker**			**Beta-blocker**	**No beta-blocker**			
Primary endpoint									
All-cause death, nonfatal reinfarction and heart failure admission	149 (20.8)	119 (16.3)	4.47 (0.03-8.92)	1.27 (1.00-1.62)	167 (24.3)	188 (27.4)	-3.04 (−8.42-2.34)	0.89 (0.72-1.10)	.027
Secondary endpoints									
All-cause death	77 (10.5)	57 (7.7)	2.82 (−0.25-5.90)	1.37 (0.97-1.93)	84 (11.9)	96 (13.6)	−1.61 (−5.34-2.11)	0.88 (0.66-1.18)	.054
Nonfatal reinfarction	70 (9.7)	56 (7.7)	2.07 (−0.97-5.11)	1.27 (0.89-1.80)	73 (10.6)	87 (12.6)	−2.02 (−5.61-1.58)	0.84 (0.62-1.15)	.087
Heart failure admission	13 (1.8)	11 (1.5)	0.29 (−1.01-1.60)	1.20 (0.54-2.67)	26 (3.7)	33 (4.7)	−0.98 (−3.12-1.17)	0.79 (0.47-1.33)	.40
Cardiac death	28 (3.8)	20 (2.7)	1.12 (−0.72-2.97)	1.42 (0.80-2.52)	37 (5.3)	37 (5.2)	0.04 (−2.35-2.43)	1.01 (0.64-1.59)	.36
Sustained ventricular tachycardia	2 (0.3)	1 (0.1)	0.14 (−0.32-0.60)	2.03 (0.18-22.36)	1 (0.1)	1 (0.1)	0.00 (−0.39-0.39)	1.01 (0.06-16.12)	.71
Ventricular fibrillation	2 (0.3)	2 (0.3)	0.00 (−0.53-0.53)	1.01 (0.14-7.17)	1 (0.1)	3 (0.4)	−0.28 (−0.84-0.27)	0.34 (0.03-3.23)	.46
Resuscitated cardiac arrest	4 (0.5)	1 (0.1)	0.41 (−0.19-1.01)	4.08 (0.46-36.54)	0 (0.0)	3 (0.4)	−0.42 (−0.90-0.06)	0.00 (0.00-0.00)	-

Tertiary safety endpoint									
Admission for stroke	13 (1.8)	15 (2.0)	-0.25 (−1.66-1.16)	0.88 (0.42-1.84)	24 (3.4)	10 (1.4)	2.02 (0.39-3.65)	2.43 (1.16-5.08)	.053

95%CI, 95% confidence interval; HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Hazard ratios were estimated using Cox proportional hazards models with an interaction between MI type and treatment arm and estimate the effect of taking beta-blocker vs no beta-blocker. P values were calculated using likelihood ratio tests.

FIGURE LEGENDS

Figure 1. Kaplan-Meier plot for primary endpoint. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Figure 2. Kaplan-Meier plot for the individual component of the primary endpoint. NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Figure 3. Subgroup analysis of the primary composite outcome all-cause death, nonfatal reinfarction and heart failure admission in patients with STEMI index MI. 95%CI, 95% confidence interval; AMI, acute myocardial infarction; BB, beta-blocker; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Figure 4. Subgroup analysis of the primary composite outcome all-cause death, nonfatal reinfarction and heart failure admission in patients with NSTEMI index MI. 95%CI, 95% confidence interval; AMI, acute myocardial infarction; BB, beta-blocker; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

Figure 5. Central illustration. Beta-blocker therapy at discharge after STEMI and NSTEMI stratified by LVEF. Central illustration shows the association between beta-blocker prescription at hospital discharge and long-term outcomes in patients with STEMI and NSTEMI. In STEMI, beta-blocker use was associated with a higher risk overall, driven by patients with LVEF ≥ 50%, with no significant association in those with LVEF 40% to 49%. In NSTEMI, no overall association was observed; however, beta-blockers were associated with lower risk in patients with LVEF 40% to 49%, with no significant effect in those with LVEF ≥ 50%. HR with 95%CI are shown. 95%CI, 95% confidence interval; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Figure 1.

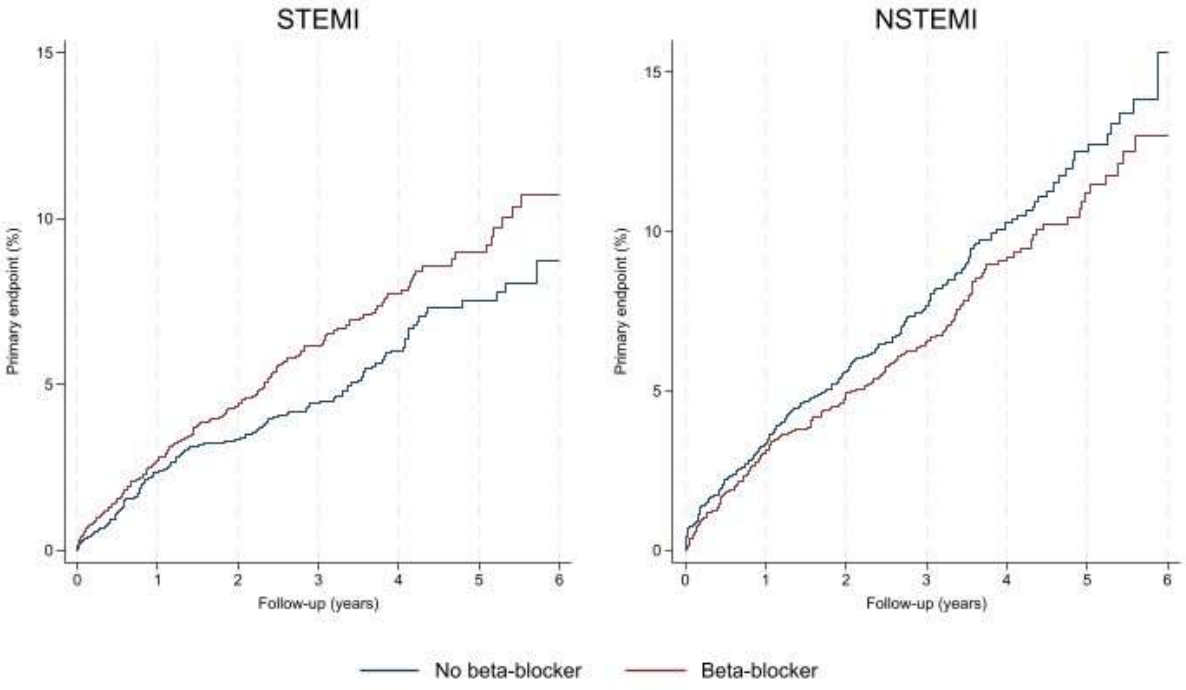

Figure 2.

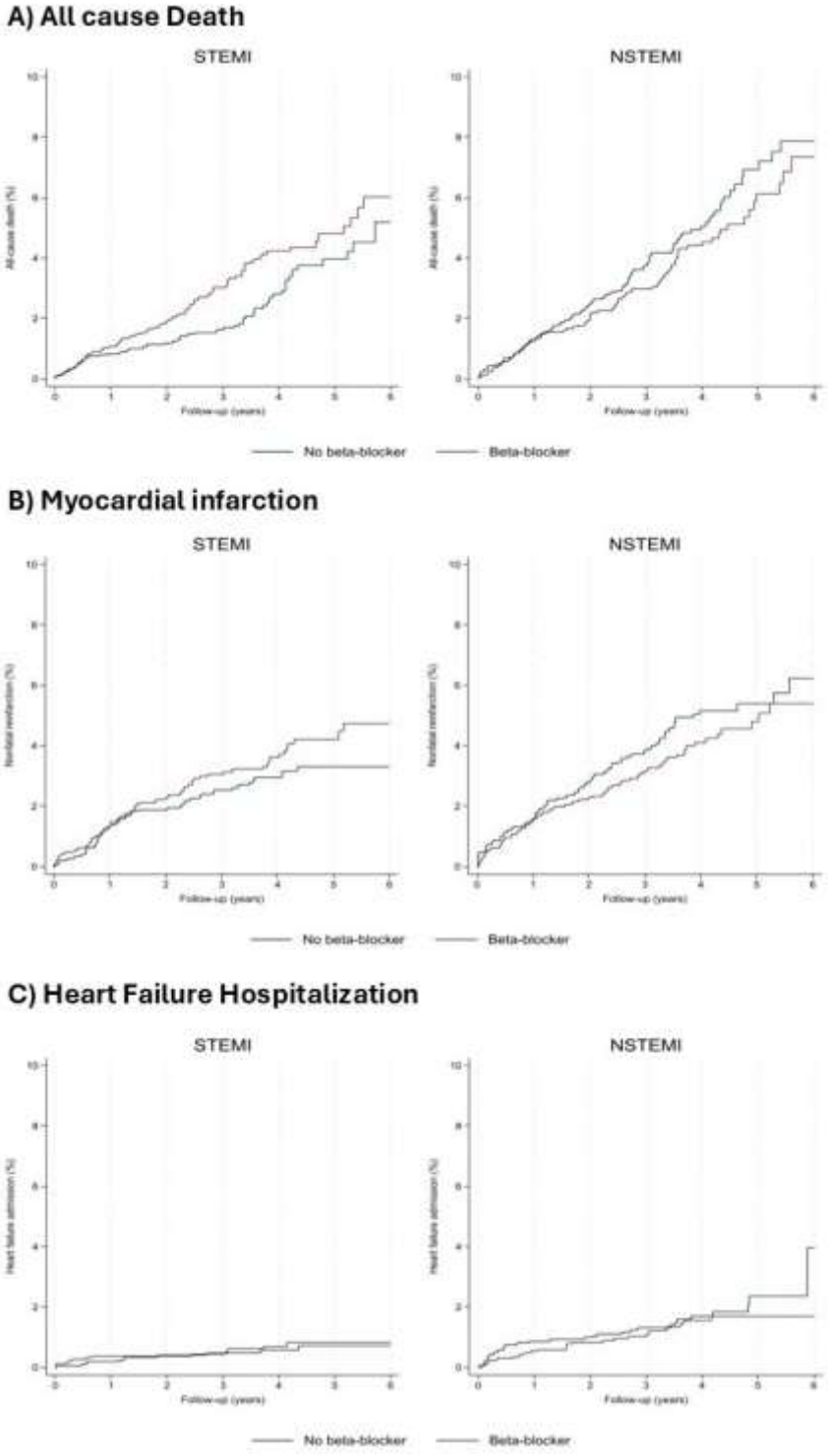

Figure 3.

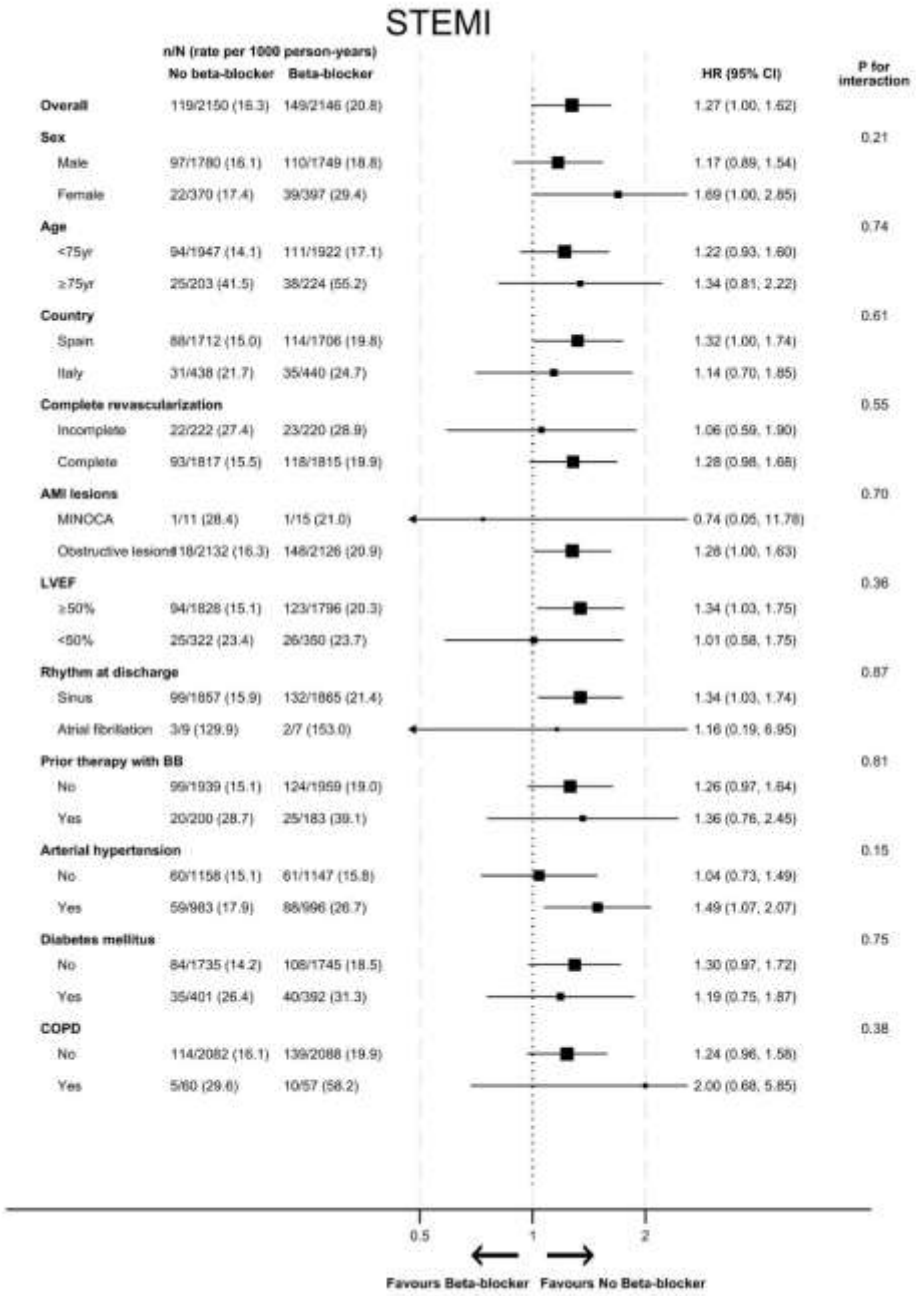

Figure 4.

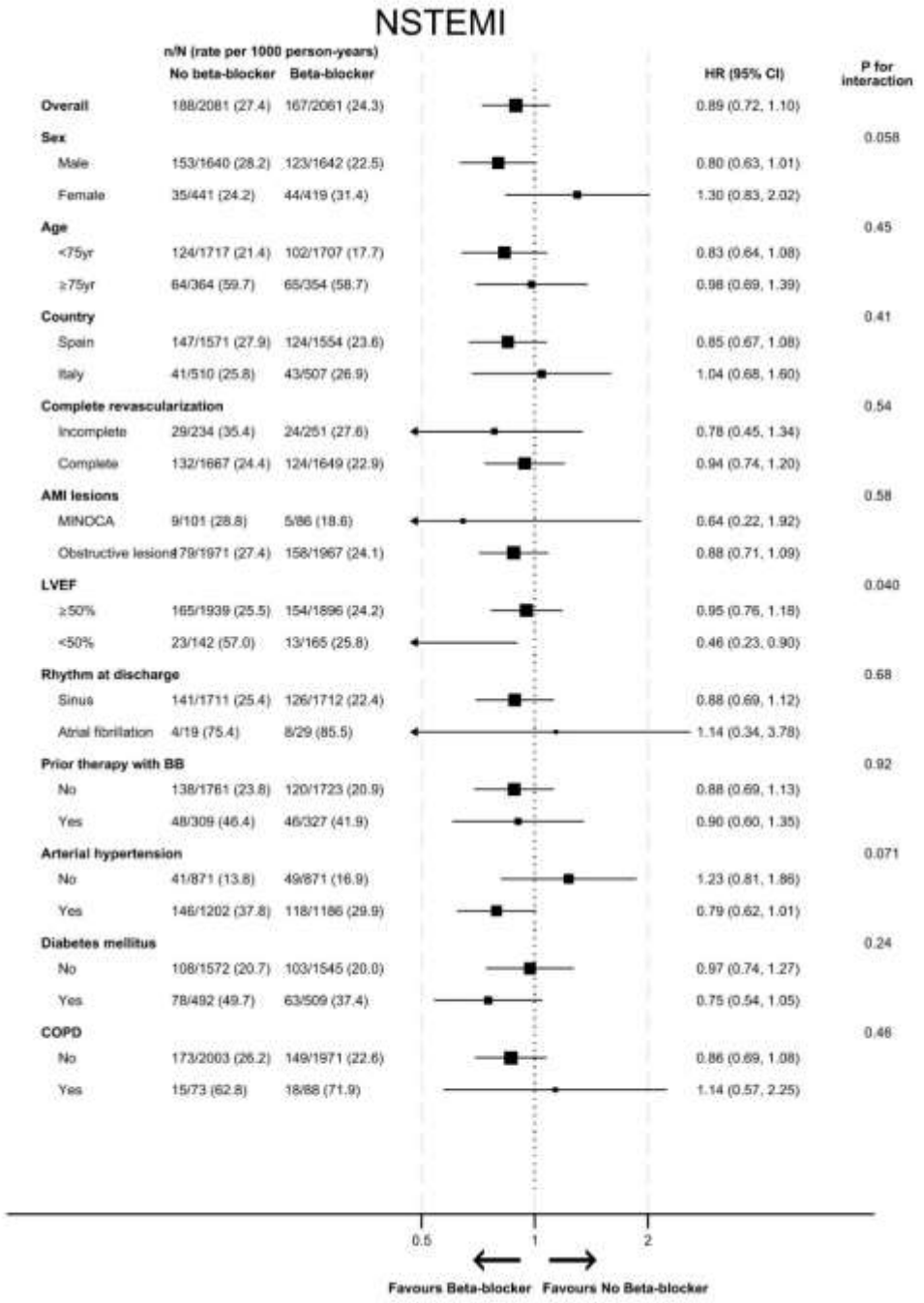

Figure 5. Central illustration.