# Comparison of Outcomes with or without Beta-Blocker Therapy After Acute Myocardial Infarction in Patients Without Heart Failure or Left Ventricular Systolic Dysfunction (from the Acute Coronary Syndromes Israeli Survey [ACSIS])

Aref El Nasasra, MD[a,*], Roy Beigel, MD[b], Robert Klempfner, MD[b], Hilmi Alnsasra, MD[a], Shlomi Matetzky, MD[b], Zaza Iakobishvili, MD[c], Ronen Rubinshtein, MD[d], Majdi Halabi, MD[e], Alex Blatt, MD[f], and Doron Zahger, MD[a]

**The contemporary benefit of routine beta-blocker therapy following myocardial infraction in the absence of heart failure or left ventricular systolic dysfunction is unclear. We investigated the impact of beta-blockers on post myocardial infarction outcome in patients without heart failure or left ventricular systolic dysfunction among patients enrolled in the biennial Acute Coronary Syndrome Israeli Surveys. MACE rates at 30 days and overall mortality at one year were compared among patients discharged on beta-blockers versus not, after multivariate analysis to adjust for baseline differences. Between the years 2000 to 2016, data from 15.211consecutive ACS patients were collected. Of 7,392 patients who met the inclusion criteria, 6007 (79.9%) were discharged on beta-blocker therapy. Prescription of beta-blockers at discharge increased modestly from 32% to 38% over the 16-year period. The 30-day MACE rates were similar in patients on vs. not on beta-blockers at discharge (9.0% and 9.5%, respectively). One year survival did not differ significantly between those on vs. not on beta-blockers (HR 0.8, 95% CI 0.58 to 1.11, p = 0.18). In conclusion, beta-blocker therapy did not affect 30 days MACE or 1-year survival after myocardial infarction in patients without heart failure or reduced ejection fraction.**  **(Am J Cardiol 2021;143:1−6)**

Studies performed in the prereperfusion era demonstrated the benefit of beta-blockers following myocardial infarction (MI).[1-3] However, over the past 3 decades the introduction of early coronary reperfusion as well as effective adjunctive therapies have dramatically changed the natural history of MI. Although the benefit of beta-blockers among patients with left ventricular systolic dysfunction (LVSD) has been confirmed in the reperfusion era,[4] the benefit among those with preserved left ventricular (LV) function is far less obvious. The historic studies of post MI beta-blockers did not differentiate between those with preserved or impaired LV function. Consequently there is very limited data regarding the efficacy of beta-blockers in contemporary acute MI patients who do not have LVSD or HF. The introduction of routine echocardiography now allows the separate study of patients who have preserved ventricular function. We aimed to estimate the clinical benefits of beta-blocker therapy on 1-year mortality among patients with acute coronary syndrome (STEMI and NSTEMI) without reduced LVEF and/or clinical signs of HF in the acute coronary syndrome Israeli Surveys (ACSIS).

## Methods

We collected data from the ACSIS survey conducted between the years 2000-2016. Briefly, the ACSIS Registry, started in 2000, is a 2-month nationwide survey conducted biennially which prospectively collects data from all consecutive ACS admissions in all 25 coronary care units in Israel. Patient management was at the discretion of the attending physicians. Eligibility for the registry was validated before discharge from the coronary care units. Discharge diagnoses were recorded as determined by the attending physicians based on clinical, electrocardiographic, echocardiographic, and biomarker criteria. Demographic, historical and clinical data, including medical management, were recorded on pre-specified forms by dedicated study personnel. The Central Data Coordinating Center (based at the Sheba Medical Center) was responsible for the collection of all case report forms and the Israel Heart Society was responsible for keeping the survey database. Thirty-day outcomes and 1-year mortality were

[a]Department of Cardiology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer-Sheva, Israel; [b]Leviev Heart Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [c]Cardiology Department, Clalit Health Services, Tel Aviv, Israel; [d]Department of Cardiology, Edith Wolfson Medical Center, Holon and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [e]Department of Cardiology, Ziv Medical Center, Faculty of Medicine, Bar-Ilan University, Tsfat, Israel; and [f]Department of Cardiology, Kaplan Medical Center, Rehovot, Hadassah − Hebrew University School of Medicine, Israel. Manuscript received October 5, 2020; revised manuscript received and accepted December 8, 2020.

See page 5 for disclosure information.

*Corresponding author: Tel: (49) 6211-660-6297.

*E-mail address:* arefsalam@hotmail.com (A. El Nasasra).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.12.044

ascertained by hospital chart review, telephone contact and use of the Israeli National Population Registry. For the purpose of this analysis we identified patients who suffered from STEMI or NSTEMI, had no history of heart failure and had documentation of an ejection fraction (EF) of ≥40% before hospital discharge (using echocardiography, contrast LV angiography or radionuclide assessment of left ventricular function). In this subgroup we compared outcomes among patients who were discharged with or without beta-blockers. This register-based analysis of pre-existing data was conducted according to the principles expressed in the Declaration of Helsinki. The ACSIS was approved by the ethics committees of all participating centers. All patients provided written informed consent for the collection of data and subsequent analysis. End points were prespecified by the ACSIS steering committee. The diagnosis of acute myocardial infarction was made by the attending physician using all available data based on the Universal Definition of Myocardial Infarction[5–7]. Major adverse cardiovascular events (MACE) were defined as a composite of 30-day all-cause mortality, recurrent MI, recurrent ischemia, stent thrombosis, ischemic stroke and urgent revascularization. Patients were divided into 2 groups: discharged on beta-blockers versus not: discharged on beta-blockers. The primary end point was 30-day MACE. A secondary end point was all-cause mortality at 1 year. Categorical variables were expressed as percentages. Continuous variables are expressed as mean with standard deviation or as medians. Differences between the 2 groups were tested with Chi-square for categorical variables and *t*-test for continuous variables.

We analyzed and compared the outcomes according to the registry period (Early: 2000 to 2008 vs Late: 2010 to 2016). Treatment effect was further studied among subgroups of left ventricular ejection fraction (>50% and 40% to 49%), type of MI (STEMI vs NSTEMI), heart rate ≥76 beats/min and <76 beats/min and anterior wall STEMI. Cox proportional hazards regression models were used to examine the difference between the 2 groups after adjustment for age, gender, hypertension, survey period and diabetes. Results are presented as odds ratio (OR) with the appropriate 95% confidence interval (CI). All tests were 2-sided and p value $< 0.05$ was considered statistically significant. Statistical analysis was performed using R Core Team version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

Between 2000 and 2016 15.211ACS patients were included in ACSIS (Figure 1). There were 7,392 post MI patients without heart failure or LVSD, including 4580 patients with an EF above 50% and 2812 with an EF between 40-49%. The proportion of NSTEMI/UA patients was slightly higher compared with STEMI, 52.8% and 47.2% respectively. The vast majority of patients underwent PCI during the index admission. Small proportions of patients were referred for CABG or treated medically (4.6% and 8.1%, respectively). Baseline characteristics are presented in Table 1. Of the 7,392 study patients, 6007 (81.2%) were discharged from hospital on a beta-blocker. Patients discharged with beta-blocker therapy had a higher

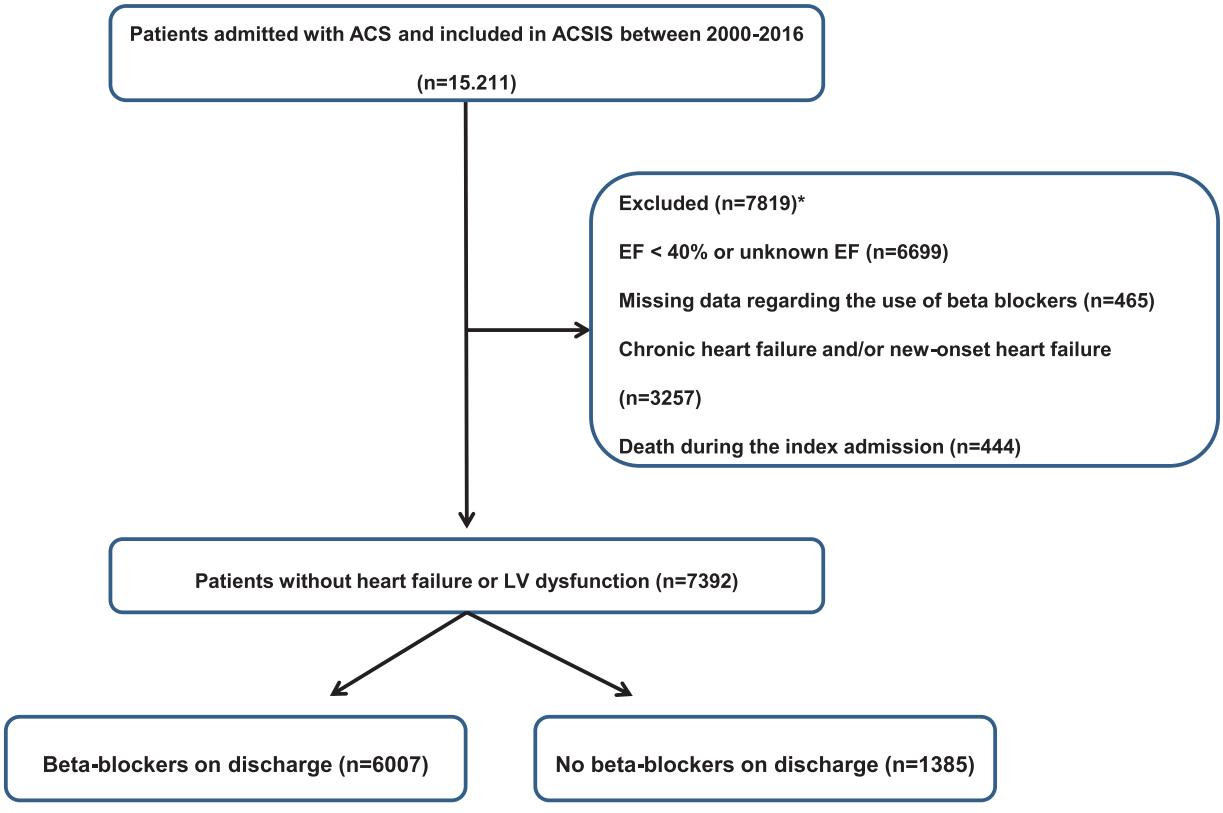


Figure 1. Study flow diagram.

Table 1
Baseline characteristics of patients on and not on beta-blocker at discharge

| | Variable Beta-blocker at discharge | | |
|---|---|---|---|
| | Yes (n=6007) | No (n= 1385) | p Value |
| Age, (years) | 60.8 ± 12.1 | 62.2 ± 13.0 | <0.001 |
| Men | (79.2%) | (78.3%) | 0.460 |
| Cardiovascular history | | | |
| Anterior wall myocardial infarction | (25.2%) | (19.1%) | <0.001 |
| Previous myocardial infarction | (23.9%) | (17.2%) | <0.001 |
| Previous coronary artery bypass grafting | (7.3%) | (5.5%) | 0.021 |
| Percutaneous coronary intervention | (24.2%) | (17.4%) | <0.001 |
| Cerebrovascular disease | (6%) | (5.9%) | 0.944 |
| Peripheral vascular disease | (5%) | (4.8%) | 0.712 |
| Cardiovascular risk factors | | | |
| Hypertension | (55.8%) | (49.8%) | <0.001 |
| Chronic renal failure | (6.1%) | (5.7%) | 0.592 |
| Diabetes mellitus | (30.8%) | (26.5%) | 0.002 |
| Dyslipidemia | (65.6%) | (60.8%) | 0.001 |
| Chronic obstructive pulmonary disease | (3.6%) | (9.4%) | <0.001 |
| Current smoker | (41.4%) | (41.7%) | 0.876 |

Continuous data are presented as mean ± standard deviation. Categorical variables are presented as number (percentage).

prevalence of anterior wall MI, were younger and had a higher prevalence of hypertension, dyslipidemia, diabetes and previous MI. The 30-days MACE rates were similar in patients on and not on beta-blockers at discharge: 9.0% and 9.5%, respectively (p = 0.54). Cumulative event rates are presented in Table 2. On univariate analysis, all-cause mortality at 1-year was significantly higher in those on beta-blockers than in those not on beta-blockers. However, this was no longer significant after multivariable adjustment (HR 0.8, 95% CI 0.58 to 1.11, p = 0.18). During the early period (2000-2008), 1 year mortality for the whole population was numerically, but not significantly lower for those on beta-blockers compared for those not on beta-blockers at discharge (Table 3).

### *Subgroup analysis*

Subgroup analyses according to left ventricular ejection fraction (>50% and 40-49%), type of myocardial infarction and heart rate ≥76 beats/min and <76 beats/min showed no significant interaction between beta-blockers at discharge and 1 year survival after adjustment for co-morbidities and survey period (Table 4).

## Discussion

Our current study shows that in a real life, nationwide prospective cohort of consecutive patients admitted with an ACS without heart failure or LVSD, beta-blocker therapy at discharge was not associated with better 30-day MACE or 1-year mortality. Moreover, no benefit of beta-blockers was found in various subgroups, including EF (>50% and 40% to 49%), type of MI or heart rate. The benefit of beta blockers following MI was established during the 1970s and 1980s. With contemporary reperfusion therapy, early revascularization and pharmacological therapy, the additional benefit conferred by beta-blockers in the absence of HF or LVSD post-MI is uncertain. Indeed, Korhonen et al[8] found a limited additional benefit for beta-blockers on survival among older post AMI patients who were adherent to statins and ACE inhibitors/ARBs.

International guidelines differ in their recommendations regarding this population. Current ESC guidelines give a class I A recommendation for beta-blockers in STEMI and NSTE-ACS patients with heart failure and/or LVSD and a Class IIA B recommendation for all STEMI patients without contraindication. No recommendation is given for beta blockers in NSTE ACS patients in the absence of heart failure, LVSD or prior MI.[9,10] In contrast, the ACC and/or AHA guidelines provide a class I A recommendation for oral beta-blockers for all patients with acute MI who do not have a contraindication.[11,12]

The COMMIT trial[3], randomized 45,852 patients with suspected acute MI to early metoprolol or placebo within

Table 2
Outcomes by beta-blocker treatment at discharge

| Variable | Total (n=7392) | Beta-blocker at discharge | | Adjusted p value |
|---|---|---|---|---|
| | | Yes (n=6007) | No (n=1385) | |
| 30-day MACE | 671 (9.1%) | 539 (9.0%) | 132 (9.5%) | 0.54 |
| 30-day mortality | 49 (0.6%) | 33 (0.6%) | 14 (1.0%) | 0.07 |
| 1-year mortality | 198 (2.7%) | 150 (2.5%) | 48 (3.5%) | 0.18 |

Major cardiovascular events (MACE) included a composite of 30-day mortality, recurrent MI, recurrent ischemia, stent thrombosis, ischemic stroke and urgent revascularization.

Table 3
Outcomes by beta-blocker treatment at discharge and survey period

| Variable | Early period 2000-2008 | | p-value | Late period 2010-2016 | | p-value |
|---|---|---|---|---|---|---|
| | Yes (n=3819) | No (n=839) | | Yes (n=2188) | No (n=546) | |
| 30-day MACE | 406 (10.6%) | 89 (10.6%) | 1.00 | 133 (6.1%) | 43 (7.9%) | 0.152 |
| 30-day mortality | 20 (0.5%) | 8 (1.0%) | 0.224 | 13 (0.6%) | 6 (1.1%) | 0.325 |
| 1-year mortality | 100 (2.6%) | 32 (3.8%) | 0.078 | 50 (2.3%) | 16 (3.0%) | 0.467 |

Table 4
HR of 1-year mortality with 95% CI by beta-blocker treatment at discharge in predefined population subgroups

| Subgroup | Patients | Beta-blocker at discharge | | Adjusted* HR for beta-blockers vs. no beta-blockers (95% CI) |
|---|---|---|---|---|
| | | Yes | No | |
| EF ≥50% | 4580 | 3600 | 980 | 0.71 (0.45-1.11) |
| EF 40-49% | 2812 | 2407 | 405 | 0.83 (0.51-1.35) |
| Anterior wall MI | 1776 | 1512 | 264 | 0.58 (0.31-1.08) |
| STEMI | 3485 | 2865 | 620 | 0.79 (0.46-1.35) |
| NSTEMI & UAP | 3904 | 3139 | 765 | 0.80 (0.53-1.20) |

* Further adjusted for co-morbidities and survey period. Consistent results were obtained when interaction term analysis was employed (all p-values for interaction >0.05).

24 hours of symptom onset and regardless of LVEF showed no mortality reduction with beta-blockers at 28 days and an increased risk of cardiogenic shock, especially during the first day after admission. Notably, this study included Killip class II and III patients (24%), who had been excluded from many previous trials. In the REACH registry[13], which included patients with an MI within 1-year, beta-blocker use was associated with lower rates of the secondary outcome (OR 0.77; 95% CI, 0.64 to 0.92), suggesting short-term benefit of beta-blockers post-MI driven by a reduction in hospitalizations or revascularization procedures. In a post-hoc analysis from the CHARISMA trial[14], beta-blockers were associated with lower rates of the primary composite outcome of nonfatal MI, stroke, and cardiovascular mortality at 28 months of follow-up in a propensity-score-matched cohort of 1,962 patients with prior MI without HF but there was no significant difference in mortality ($p = 0.20$) and results were driven primarily by lower rates of recurrent MI.

A recent meta-analysis of randomized trials[15] did not find a mortality effect associated with beta-blockers in studies from the reperfusion era, as opposed to a significant reduction in mortality for studies published in the pre-reperfusion era. In the era before reperfusion, beta-blockers use in patients with MI was associated with reduced all-cause mortality at 30 days (RR 0.87; 95% CI, 0.79 to 0.96) and at 1 year (RR 0.91; 95% CI, 0.66 to 0.98). In the reperfusion era, beta-blockers did reduce MI and angina at 30 days, but benefit seemed to be limited to the short term (30 days) and came at the expense of an increase in HF and cardiogenic shock.

In a meta-analysis of 10 observational beta-blocker studies in AMI, Huang et al[16] found that beta-blockers reduced the risk of all-cause death restricted to those with reduced ejection fraction, as well as those with lower use of other secondary preventive drugs or with non-ST-segment elevation myocardial infarction. The FAST-MI 2005 registry[17] found that persistence with beta-blockers therapy during the first year was not associated with lower 5-year mortality (adjusted HR, 1.19; 95% CI, 0.65 to 2.18) but early beta-blocker use was associated with reduced 30 day mortality. The United Kingdom MINAP registry[18], revealed that the use of beta-blockers in AMI patients without HF or reduced LVEF was not associated with lower 1-year mortality, and similar findings were observed in patients with both subtypes of MI (STEMI and NSTEMI).

In addition, a large cohort study found that discontinuation of beta-blockers beyond 1 year post AMI was not associated with higher all-cause mortality.[19] In contrast, a recent large meta-analysis comprising 189,385 post MI patients with a median LVEF of 53.7% found that the use of oral beta-blockers was associated with a reduction in all-cause mortality at a median follow-up of 2.7 years.[20] These studies included both patients with LVSD and preserved LV function. Data on LV function were only available in 10 out of the 16 included studies.

Finally, a nationwide registry including 28,970 patients who underwent coronary revascularization for AMI reported that patients receiving beta blocker for ≥1 year had a significantly lower risk of all-cause death than those receiving beta-blockers for <1 year [HR 0.5 (95% CI 0.46 to 0.55, $p < 0.001$].[21] However, these findings must be interpreted with caution because patients with a history of heart failure were excluded and information on ejection fraction was not available. There are no randomized studies specifically evaluating the efficacy of beta-blockers on mortality in post-MI patients without heart failure or LVSD. Ongoing randomized clinical trials, the REBOOT [NCT03596385], DANBLOCK [NCT03278509] and AbYSS [NCT03498066] may clarify this gap.

The reason for the lack of benefit of beta-blockers in contemporary post MI patients with preserved systolic function may be attributed to a number of factors. The benefit of beta-blockers is mostly derived from their ability to mitigate left ventricular remodeling and to lower the risk of sudden death. Both these risks are extremely small among patients with preserved systolic function. Moreover, the routine use of echocardiography now allows the identification of patients with preserved LV function, while many historical studies did not have this ability and post MI patients were analyzed regardless of LV function. Furthermore, modern reperfusion, revascularization and pharmacotherapy have dramatically improved outcome post MI. In our study, 1 year mortality among post MI patients with preserved LV systolic function was about 2.5%. This very low mortality is very difficult to improve upon.

The present study has several limitations that should be acknowledged. It is observational and as such uncontrolled confounding cannot be ruled out. Nevertheless, data collection was prospective, included all consecutive patients and based on a standard case report form using standardized definitions. Another limitation is that we do not have data on the use of beta-blockers during follow-up.

In Conclusion, in a nationwide survey of all AMI patients, beta-blocker therapy did not alter 30-day MACE

or 1-year mortality post MI in patients without heart failure or reduced ejection fraction. The issue of the efficacy of beta-blockers in patients in the absence of HF or reduced LVEF is 1 of the major gaps in evidence in post MI management. Contemporary dedicated large randomized clinical trials are needed to further guide adequate management.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

## Credit Author Statement

Author agreement/statement: Aref El Nasasra, MD: writing original draft, completion final draft and editing. Roy Beigel, MD: writing review and editing. Robert Klempfner, MD: writing review; Hilmi Alnsasra, MD: writing review and editing; Shlomi Matetzky, MD: writing review. Zaza Iakobishvili, MD: writing review. Ronen Rubinshtein, MD: writing review. Majdi Halabi, MD: writing review. Alex Blatt, MD: writing review; Doron Zahger, MD: Conceptualization, Methodology, writing review and editing.


1. Viscoli C M, Horwitz R I, Singer B H. Beta-blockers after myocardial infarction: influence of first-year clinical course on long-term effectiveness. *Ann Intern Med* 1993;118:99–105.
2. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318:1730–1737.
3. Chen Z M, Pan H C, Chen Y P, Peto R, Collins R, Jiang L X, Xie J X, Liu L S. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1622–1632.
4. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385–1390.
5. Alpert J S, Thygesen K, Antman E, Bassand J P, The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959–969.
6. Thygesen Kristian, Alpert Joseph S, White Harvey D. Joint ESC/ACCF/AHA/WHF task force for the redefinition of myocardial infarction; Joint ESC/ACCF/AHA/WHF task force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525–2538.
7. Thygesen Kristian, Alpert Joseph S, Jaffe Allan S, Simoons Maarten L, Chaitman Bernard R, White Harvey D. The writing group on behalf of the joint ESC/ACCF/AHA/WHF task force for the universal definition of myocardial infarction. *Circulation* 2012;126:2020–2035.
8. Korhonen MJ, Robinson JG, Annis IE, Hickson RP, Bell JS, Hartikainen J, Fang G. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. *J Am Coll Cardiol* 2017;70:1543–1554.
9. Collet Jean-Philippe, Thiele Holger, Barbato Emanuele, Barthélémy Olivier, Bauersachs Johann, Bhatt Deepak L, Dendale Paul, Dorobantu Maria, Edvardsen Thor, Folliguet Thierry, Gale Chris P, Gilard Martine, Jobs Alexander, Jüni Peter, Lambrinou Ekaterini, Lewis Basil S, Mehilli Julinda, Meliga Emanuele, Merkely Béla, Mueller Christian, Roffi Marco, Rutten Frans H, Sibbing Dirk, Siontis George CM. SC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2020;00:1–79.
10. 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. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–177.
11. O'Gara PT, Kushner FG, Ascheim DD, Jr Casey DE, 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, TamisHolland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW. 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. *J Am Coll Cardiol* 2013;61:e78–e140.
12. 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. 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:e139–e228.
13. Bangalore Sripal, Steg Gabriel, Deedwania Prakash, Crowley Kevin, Eagle Kim A, Goto Shinya, Magnus Ohman E, Cannon Christopher P, Smith Sidney C, Zeymer Uwe, Hoffman Elaine B, Messerli Franz H, Bhatt Deepak L. REACH Registry Investigators. $\beta$-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;308:1340–1349.
14. Bangalore Sripal, Bhatt Deepak L, Steg Ph Gabriel, Weber Michael A, Boden William E, Hamm Christian W, Montalescot Gilles, Hsu Amy, Fox Keith A A. A Michael Lincoff. $\beta$-blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. *Circ Cardiovasc Qual Outcomes* 2014;7:872–881.
15. Bangalore S, Makani H, Radford M, Thakur K, Toklu B, Katz SD, DiNicolantonio JJ, Devereaux PJ, Alexander KP, Wetterslev J, Messerli FH. Clinical outcomes with beta-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J *Med* 2014;127:939–953.
16. Huang BT, Huang FY, Zuo ZL, Liao YB, Heng Y, Wang PJ, Gui YY, Xia TL, Xin ZM, Liu W, Zhang C, Chen SJ, Pu XB, Chen M, Huang DJ. Meta-analysis of relation between oral beta-blocker therapy and outcomes in patients with acute myocardial infarction who underwent percutaneous coronary intervention. *Am J Cardiol* 2015;115:1529–1538.
17. Puymirat Etienne, Riant Elisabeth, Aissoui Nadia, Soria Angèle, Ducrocq Gregory, Coste Pierre, Cottin Yves, Aupetit Jean François, Bonnefoy Eric, Blanchard Didier, Cattan Simon, Steg Gabriel, Schiele François, Ferrières Jean, Juillière Yves. Tabassome Simon, Nicolas Danchin. $\beta$ blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *BMJ* 2016;354:i4801.
18. Dondo Tatendashe B, Hall Marlous, West Robert M, Jernberg Tomas, Lindahl Bertil, Bueno Hector, Danchin Nicolas, Deanfield John E, Hemingway Harry, Fox Keith A A, Timmis Adam D, Gale Chris P. $\beta$-Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;69:2710–2720.
19. Neumann Anke, Maura Géric, Weill Alain, Alla François, Danchin Nicolas. Clinical events after discontinuation of $\beta$-Blockers in patients without heart failure optimally treated after acute myocardial infarction: a cohort study on the french healthcare databases. *Circ Cardiovasc Qual Outcomes* 2018;11:e004356.
20. Dahl Aarvik Magnus, Sandven Irene, Dondo Tatendashe B, Gale Chris P, Ruddox Vidar, Munkhaugen John, Atar Dan, Otterstad Jan Erik. Effect of oral b-blocker treatment on mortality in contemporary post-

myocardial infarction patients: a systematic review and meta-analysis. *Eur Heart J Cardiovasc Pharmacother* 2019;5:12–20.

21. Kim Jihoon, Kang Danbee, Park Hyejeong, Kang Minwoong, Park Taek Kyu, Lee Joo Myung, Yang Jeong Hoon, Song Young Bin, Choi Jin-Ho, Choi Seung-Hyuk, Gwon Hyeon-Cheol, Guallar Eliseo, Cho Juhee, Hahn Joo-Yong. Long-term b-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. *Eur Heart J* 2020;0:1–9.