Since the 1980s, the mortality from myocardial infarction (MI) has regressed by approximately 25% in Western countries, not only due to the development of routine defibrillation, monitored units and early coronary reperfusion but also to the introduction of antiplatelet therapies, angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs), statins and beta-blockers. The reperfusion era started in the 1980s, when thrombolytic therapy gained wide acceptance in ST-segment elevation myocardial infarction (STEMI) after several randomized controlled trials showed reduced mortality and better preservation of left ventricular ejection fraction (LVEF) with thrombolysis over standard treatment. Thereafter, randomized studies performed from the late 1990s and aggregated in the meta-analysis of Keeley in 2003 (1), showed the superiority of primary percutaneous coronary intervention (PPCI) over thrombolysis in STEMI. According to recent guidelines, PPCI is the treatment of choice for STEMI, when available in a maximum expected delay from diagnosis to wire crossing the lesion of 120 minutes (ideally 90 minutes for transferred patients and 60 minutes for patients presenting at PPCI centers) (2). An early invasive approach—defined as coronary angiography within 24 hours of first medical contact—is recommended for non-ST segment elevation MI (NSTEMI) (3).

Since the first studies showing a survival benefit of beta-blockers in patients with non-reperfused acute MI (4,5), timely reperfusion has changed the landscape not only because of a reduction in early mortality and mechanical complications, but also because of more favorable myocardial healing and remodeling, translating into improved LVEF, less heart failure, and a myocardium less vulnerable to arrhythmias. Beta-blockers slow heart rate and have a negative inotropic effect, leading to a reduction in myocardial oxygen consumption and increasing the threshold to myocardial ischemia. In chronic stable angina, the efficacy of beta-blockers in reducing angina and complications of myocardial ischemia including infarction, arrhythmias and sudden death has been shown in randomized trials (6,7). In this respect, it has been hypothesized that the decrease in out-of-hospital ventricular fibrillation and the increase in out-of-hospital pulseless electrical activity/asystole observed in Holland over the last 10 years is related to long term post-MI treatment with beta-blockers and intracardiac defibrillators (8). In post MI patients with a LVEF ≤40% or heart failure—in the absence of contraindications such as acute heart failure, hemodynamic instability or high degree AV block—beta-blockers have a class I indication (9). Indeed, in 2001 the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) (10) trial—a randomized study comparing carvedilol to placebo in a post-MI population with half of the patients reperfused and a LVEF ≤40%—demonstrated a 23% reduction in all-cause mortality with beta-blockers at 2.5 years. Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) randomized 45,852 Chinese patients with acute MI (STEMI, left-bundle branch block, or ST depression) within 24 hours of symptom onset and regardless of
the LVEF, to metoprolol (intravenous administration followed by 200 mg per os daily) or placebo (11). The vast majority of patients did not undergo timely reperfusion. There was no mortality reduction with beta-blockers at 28 days. Patients treated with metoprolol had fewer reinfarction and ventricular fibrillation episodes, but the benefit was counterbalanced by an increase in cardiogenic shock. An excess in mortality in the active treatment arm was observed among patients who were hypotensive or in Killip class III.

There are several unanswered questions with respect to beta-blockers post MI, in particular the timing and duration of administration, the optimal dose and the benefit in patients with normal or mildly depressed LVEF. In animal models of acute MI, metoprolol markedly reduced infarct size when administered IV before reperfusion (12). The Early Intravenous Beta-Blockers in Patients With STEMI segment Coronary Intervention (EARLY-BAMI) trial (13)—a double-blind randomized trial of IV metoprolol (5 mg at recruitment and 5 mg before PPCI) or placebo in more than 600 STEMI patients within 12 h of symptom onset—did not show a reduction of MI size on magnetic resonance imaging (MRI), but beta-blockers significantly decreased the incidence of malignant arrhythmias in the acute phase in the absence of adverse events. Killip class III or IV, systolic blood pressure <100 mmHg, heart rate <60 beats per min, type II or III AV blocks were all exclusion criteria for the study. The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction [METOCARD-CNIC (14,15)] trial—a randomized but not blinded nor placebo-controlled trial including 131 patients in the metoprolol 15 mg arm and 130 in the control group who had anterior STEMI within 6 hours of symptom onset, were in Killip class I or II and had a systolic blood pressure >120 mmHg—did show smaller MI size on MRI and higher LVEF in the metoprolol arm at 5 to 7 days post MI with no excess of adverse events during the first 24 hours. All patients without contraindications received oral metoprolol within 24 hours. At 6-month follow-up, the early IV metoprolol group showed higher LVEF, reduced incidence of severe LV dysfunction as well as ICD indication. Furthermore, in the early IV metoprolol group there were fewer re-admissions for heart failure.

According to the latest ESC STEMI guidelines, IV beta-blockers at the time of presentation followed by oral treatment should be considered, in the absence of contraindications, in patients undergoing PPCI with no signs of acute heart failure (Killip class ≤ II) and a systolic blood pressure >120 mmHg [class IIa, level of evidence (LOE) B]. The 2013 ACC/AHA STEMI guidelines (16) recommend that beta-blockers should be started in the first 24h in patients with STEMI (class I, LOE B), if there are no signs of heart failure, evidence of low-output state, increased risk for cardiogenic shock or other contraindications (PR interval >0.24 s, II or III degree heart block, active asthma, or reactive airways disease). In the ESC NSTEMI guidelines, early initiation of beta-blockers is recommended in patients with ongoing ischemic symptoms and in the absence of contraindications (class I, LOE B) (3). Furthermore, beta-blockers should not be administered in patients with possible coronary spasm or cocaine use since they might favor spasm by leaving alpha-mediated vasoconstriction unopposed by beta-mediated vasodilatation. In accordance with the guidelines, the prescription of beta-blockers in post-MI patients is high even in patients without LV dysfunction. A 2015 meta-analysis of 10 observational acute MI studies including more than 40,000 patients showed that beta-blockers reduced the risk of all-cause death (17). However, the benefit of these agents was not found in all subgroups and seemed confined to the patients with reduced LVEF, with low use of other secondary prevention drugs, or NSTEMI.

Dondo et al. tried to answer the question of the benefit of beta-blockers in patients post MI with no LV systolic dysfunction (18). They reported in the Journal of the American College of Cardiology earlier in 2017 the impact of the use of beta-blockers on all-cause mortality at 1-year in MI survivors without heart failure or LV systolic dysfunction in the United Kingdom national heart attack register, known as Myocardial Ischaemia National Audit Project (MINAP). Data were prospectively collected at each hospital between January 2007 and June 2013, and transferred online (encrypted) to a central database. Strengths of the study included the large sample size (analytic cohort of 179,810 patients) and the broad use of evidence-based treatments (revascularization rate >50%, >90% dual antiplatelet therapy, >80% ACEI/ARBs, >80% participating in a rehabilitation program, 95% received beta-blockers). A higher unadjusted mortality rate at one year was observed in the patients not receiving beta-blockers (4.9% vs. 11.2%). However, in a propensity score analysis including 24 variables, there was no difference in mortality in patients discharged with or without beta-blockers.

These data should be interpreted with great caution. First it may be argued that the two groups (no beta-
blocker vs. beta-blocker) may not be at all comparable, despite the statistical adjustments. Indeed, the populations were imbalanced in terms of size (5% vs. 95% of the cohort, respectively) and major differences were present in the baseline characteristics (e.g., mean age difference between the groups > 5 years). Furthermore, patients not receiving or receiving beta-blockers were managed differently with respect to all the other evidence-based therapies (i.e., aspirin, P2Y₁₂ inhibitors, ACE inhibitors, statins, coronary angiography, revascularization as well as cardiac rehabilitation). Therefore, it might not be surprising that the one-year mortality rates of patients not treated vs. treated with beta-blockers were not in the same range. Multivariable/propensity score analyses may have incompletely adjusted for the differences and there may have been unmeasured co-variates affecting mortality. In this setting, adjustment with sophisticated statistical methods may have been methodologically sound but clinically questionable. Second, patients with a LVEF from 30% to 40%, for whom there are clear benefits in prescribing beta-blockers, were included in the study. Third, no information on adherence to beta-blocker treatment was available, as the prescription of beta-blockers was recorded only at hospital discharge. In this respect, the Outcomes of Beta-blockers Therapy After Myocardial Infarction [OBTAIN (19)] study—a North American registry of more than 7,000 patients with acute MI—showed that at 2 years, 20% of the patients on beta-blockers had a lower dose than at discharge, 54% had the same dose, 3.8% had discontinued their treatment and the mean overall dose was 38% of the optimal dose.

The issue of the efficacy of beta-blockers in patients with preserved/mildly reduced LV function is one of the major gaps in evidence in post MI management. Let’s just think at the potential impact on male patients with respect to erectile dysfunction while in both genders it may be challenging to differentiate post-MI fatigue or even depression from a potential side-effect of this class of agents (20-23). The results of the study from Dondo et al. are to be considered hypothesis-generating and not sufficient to change practice. In the era of PPCI, there may be little room for further risk reduction in patients post MI with normal LVEF in the presence of guideline-based therapy with antiplatelet treatment, statins, and ACE inhibitors/ARBs. Randomized studies assessing the efficacy of beta-blockers on mortality in patients with normal or slightly decreased LVEF are lacking. Given the low likelihood that the pharmaceutical industry will ever fund an adequately powered clinical trial in the field—because of the lack of return on investment—it is up to individual investigators, medical societies, public funds or foundations to invest time, energy, and money in this endeavor. Should this issue ever be solved, the next in line for post-MI patients would be the optimal duration of beta-blocker treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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