Is Long-Term Beta-Blocker Therapy for Myocardial Infarction Survivors Still Relevant in the Era of Primary Percutaneous Coronary Intervention?

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ABSTRACT: Studies on trials conducted before the use of thrombolysis demonstrated both short- and long-term benefits of beta-blockers, and one meta-analysis of those trials showed a 25% reduction in 1 year mortality. Treatment with beta-blockers was and continues to be recommended for patients after ST elevation myocardial infarction (STEMI), but many patients failed to receive these agents mostly because physicians were unconvinced of their benefit. A similar analysis of the studies in STEMI patients treated with thrombolysis also showed an overall 23% reduction in mortality associated with β-blocker use in the era of primary percutaneous coronary intervention (PCI). In the present review, we examine the relationship between the pharmacology of β-blockers and their potential utility in order to review early trials on their post-infarct efficacy and to place these findings in the context of this specific patient population in the era of primary PCI.

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KEY WORDS: acute myocardial infarction (AMI), ischemia, reperfusion, primary percutaneous coronary intervention (PCI), beta-blockers

Beta-blocker therapy has long been recommended for the treatment of ST-elevation myocardial infarction. The recent European Society of Cardiology guidelines for the management of STEMI state that oral treatment with beta-blockers is indicated in patients with heart failure or left ventricular dysfunction (Class I indication), and should be considered during hospital stay and continued thereafter in all STEMI patients for whom there are no contraindications (Class IIa indication) [1]. The 2013 American College of Cardiology Foundation/American Heart Association Guidelines for the Management of ST-Elevation Myocardial Infarction state that treatment with oral β-blockers should be initiated in the first 24 hours in patients with STEMI, and continued during and after hospitalization for all patients with STEMI with no contraindications (Class I indication). They also consider it reasonable to administer intravenous β-blockers at the time of presentation in patients with STEMI with no contraindications and who are hypertensive or have ongoing ischemia (Class IIa indication) [2].These guidelines relied on randomized controlled trials and one meta-analysis, which demonstrated beneficial effects of β-blockers on survival in STEMI patients [3-8]. Considering the wealth of information supporting the use of β-blocker therapy, it is surprising and somewhat disappointing that 30% to 50% of patients with STEMI still fail to receive those agents, a finding that may be related, in part, to the surprisingly few studies providing evidence-based data to substantiate the use of these pharmaceutical agents for STEMI patients post-primary angioplasty.

Despite evidence supporting β-blocker therapy, 30%–50% of STEMI patients still do not receive it

HOW DO β-ADRENORECEPTOR ANTAGONISTS WORK?

Beta-adrenoreceptor antagonists (β-blockers) were introduced into clinical practice at a time when understanding of the pathogenesis of acute coronary syndromes was quite limited beyond the recognition of thrombotic occlusion of vessels. It was recognized that the abolition of tachycardia together with the negative inotropic effects of these pharmaceutical agents would reduce myocardial oxygen demand in regions with occluded vessels. It was therefore postulated that β-blocker therapy might reduce infarct size. This hypothesis was tested by Peter and co-workers [9], who demonstrated that while intravenous propranolol had no effect on overall creatine kinase release, there was a reduction in CK release among a subgroup of patients treated within the first 4 hours following the onset of symptoms. However, a later and larger series of STEMI patients in the MILIS Study [10] found no evidence that propranolol limited infarct size (notably, only 2% of the patients were treated within 4 hours of symptom onset). Additional persuasive evidence, predominantly from animal models, suggested that β-blockers prevent ischemic ventricular fibrillation [11,12]. A meta-analysis of 16 clinical studies on

STEMI = ST elevation myocardial infarction

CK = creatine kinase

β-blocker use and published before the introduction of primary percutaneous coronary interventions in 1997 revealed a mean 34% reduction in risk of sudden cardiac death in the early post-infarct period [13].

β-blockers could potentially interact with processes that are now recognized to precipitate the occurrence of acute coronary syndromes, such as inflammatory activation, rupture of atheromatous plaques, platelet aggregation and associated coronary vasospasm. In general, β-blockers have no effect on markers of inflammatory activation and minimal effect on platelet aggregability [14]. There are no detailed studies on their effect on plaque stability or on various matrix metalloproteinases which appear to play pivotal roles in plaque fissure and rupture. In terms of their effect on coronary vasomotor tone, however, there is considerable evidence that β-adrenoceptor antagonists tend to increase vasomotor tone in the presence of endothelial dysfunction [15], although it remains uncertain whether this precipitates overt coronary spasm with some degree of regularity. Taken together, these lines of evidence indicate that β-blockers exert potentially beneficial effects on myocardial viability and excitability in acute myocardial infarction, but there are no data to indicate that they favorably influence the intravascular factors associated with the pathogenesis of AMI.

TRIALS INVOLVING β-BLOCKER USE IN THE PRE-REPERFUSION ERA

The case for routine β-blocker therapy for post-AMI survivors rests largely on the results of three trials conducted in the pre-thrombolytic era over 30 years ago [3-5]. What is clear from the results of those investigations is that timolol, metoprolol and propranolol decreased post-infarct mortality rates during the follow-up period of 3–24 months. Furthermore, the Goteborg Metoprolol Study [3] provided evidence for a positive β-blocker effect on the incidence of both early (during initial hospitalization) and late (up to 3 months of follow-up) post-infarction tachyarrhythmias. In addition, the Norwegian Timolol study [4] documented a highly significant (approximately 30%) reduction in the rate of re-infarction, and the BHAT trial [5] reported an approximately 15% decrease in re-infarction. Clinical data from these early studies are incomplete. In particular, there are no definitive data on LV function. However, approximately 4% of patients in the Norwegian Timolol study [4] had a history of congestive heart failure, compared to approximately 15% in the BHAT trial [5].

The rationale for long-term β-blockade in STEMI patients after successful primary percutaneous coronary interventions and uncomplicated hospitalization is uncertain

The effects of β-blockers on early mortality post-infarct were evaluated in two other large randomized studies. While the results of the MIAMI study (utilizing metoprolol as the β-blocker) were inconclusive [6], the ISIS-1 study (utilizing atenolol as the β-blocker) showed a small but significant reduction in vascular mortality rates [7]. Importantly, neither of the two latter studies showed any significant difference in the rates of re-infarction or of non-fatal tachyarrhythmias.

While these early results are of obvious importance, the studied populations of STEMI patients could be considered as being undertreated by current standards. The two major differences between the time those trials were conducted and the current standard of care are the lack of any acute reperfusion strategy, whether via angioplasty or thrombolysis, and the lack of angiotensin-converting enzyme inhibitors and statins for post-MI therapeutic management.

An important issue that needed exploration was whether β-blockers will have any additional beneficial long-term effects in patients in whom LV systolic function is largely intact post-infarct and/or in whom there is no major residual myocardial ischemic area. Two sub-analyses of the BHAT database addressed that issue. Viscoli et al. [16] evaluated the time course of cardiac events post-AMI and the long-term efficacy of propranolol therapy. The hypothesis they tested was that long-term risk can be stratified in those patients on the basis of events occurring in the first year post-infarction, including recurrent ischemia, dyspnea or major tachyarrhythmias. Based on that assumption, 383 patients (~12% of the BHAT cohort) were identified as being at high risk: they demonstrated a 14% two-year mortality risk compared to a risk of less than 5% for the remaining ~88% of patients. Furthermore, while propranolol therapy was associated with a ~43% improvement in mortality over 2 years among those high risk patients, there was no evidence of a long-term beneficial effect of that β-blocker in the remaining patients. Further analyses also revealed no beneficial effects of propranolol or metoprolol on a non-Q-wave infarction subset of patients, with no additional effects on re-infarction [17,18].

Goldman et al. [19] analyzed the costs and effectiveness of routine therapy with β-adrenergic antagonists in patients who survived an AMI. Their study findings suggested that routine β-blocker therapy showed a relatively favorable cost-effectiveness ratio in medium and high risk patients but not in low risk patients.

EARLY β-BLOCKER THERAPY IN POST-THROMBOLYSIS/PCI PATIENTS

In 1991, Roberts et al. [20] reported the results of the TIMI II-B study of 1434 STEMI patients who received thrombolytic therapy. The patients were randomized to receive either intravenous metoprolol at admission followed by oral therapy, or metoprolol therapy beginning on day 6. No differences in pre-discharge

AMI = acute myocardial infarction
LV = left ventricular

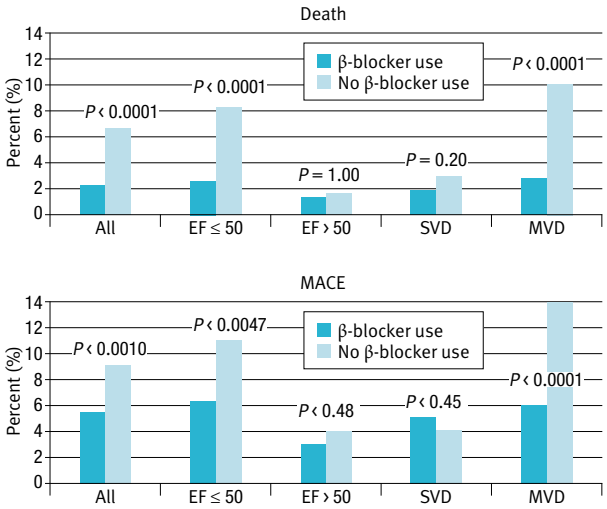
PCI = percutaneous coronary intervention

Table 1. Major effects of early metoprolol therapy in the COMMIT study [21]

Outcome measure	Odds ratio (95% CI)	*P*
Death	0.99 (0.92–1.05)	NS
Re-infarction	0.82 (0.72–0.92)	0.001
Ventricular fibrillation	0.83 (0.75–0.93)	0.001
Cardiogenic shock	1.30 (1.15–1.41)	0.0001

CI = confidence interval

Figure 1. Six month clinical outcomes in PAMI study groups



EF = ejection fraction, MACE = major adverse cardiac events, MVD = multivessel disease, SVD = single-vessel disease. From [25] with permission from Elsevier (#3036371067566)

global or regional LV function were observed between the groups, but metoprolol at admission reduced the incidence of re-infarction (a secondary end-point of the study). Importantly, this cohort comprised patients with uncomplicated myocardial infarctions who had relatively well-preserved LV systolic function post-infarct. The results of the COMMIT study [21] were published in 2005 and included a very large patient population (45,852 patients), 93% with presumptive STEMI. It also addressed the issue of putative beneficial effects of early metoprolol therapy in the reperfusion era. In that trial, metoprolol had no significant effect on early mortality (primary end-point) and, although it reduced the risk of re-infarction and of early ventricular fibrillation, that β-blocker also increased the risk of cardiogenic shock [Table 1], with the risk of hemodynamic deterioration greatest among initially unstable patients.

The CAPRICORN study [22] focused on the effects of carvedilol in 1959 post-MI patients with LV ejection fractions ≤ 40% and produced equivocal results, with non-significant reductions in the end-points of all-cause mortality and hospital admission. Halkin et al. [23] evaluated the effect of β-blockers on 30 day mortality in the 2082 patients undergoing primary PCI for STEMI as part of the CADILLAC trial (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications), a randomized trial of balloon angioplasty versus stenting with or without the glycoprotein IIb/IIIa agent, abciximab. The study results demonstrated a lower 30 day mortality in the β-blocker group (1.5% vs. 2.8%, $P = 0.03$). No improvement in survival was achieved at 1 year. The lack of long-term benefit, however, might have been due to the high percentage of patients in both groups who received β-blockers during follow-up (86% who were initial β-blocker users vs. 70% who were not).

Current guidelines support the use of β-blockers in all eligible myocardial infarction survivors, regardless of revascularization strategy

LONG-TERM β-BLOCKER THERAPY FOLLOWING SUCCESSFUL PRIMARY PCI

Only a few studies have examined the benefit of β-blocker therapy in patients who underwent primary angioplasty. One was a retrospective review of the Primary Angioplasty in Myocardial Infarction (PAMI) studies that demonstrated improved outcome with β-blocker use [24]. That study pooled 2537 patients enrolled in four PAMI studies, and the patients who received β-blocker treatment before undergoing primary angioplasty were compared with those without pretreatment. After adjustment for baseline differences, a significantly lower incidence of in-hospital death was found in the group that received β-blocker therapy (1.3% vs. 3.7%, $P = 0.0035$). A strong trend toward a lower 1 year mortality was also reported ($P = 0.055$); however, not all patients received β-blockers during the follow-up period (66% to 89%). When only those who did receive β-blockers during follow-up were analyzed, there was a significantly improved 1 year mortality rate associated with its use (odds ratio = 0.43, $P = 0.001$). Kernis et al. [25] evaluated the effect of post-primary PCI β-blocker use on 6 month outcomes among 2442 patients who also participated in four of the PAMI studies (this was a slightly different cohort from the group in the previous report). The findings of their study were remarkably similar to the earlier one [24]: there was a significant reduction in mortality (2.2 vs. 6.6, $P > 0.001$), and multivariate analysis demonstrated an OR similar to that of the first study (OR = 0.43, $P = 0.0016$). Importantly, Kernis et al. [25] showed that the survival benefit was confined to high risk subgroups, such as those with EF < 50% (OR = 0.34, $P > 0.0001$) and those with multivessel disease (OR = 0.26, $P < 0.001$) [Figure 1].

The long-term effect of β-blocker therapy among STEMI patients who underwent primary PCI and who participated

OR = odds ratio
EF = ejection fraction

in the j-Cypher registry was evaluated by Ozasa et al. [26]. Mortality at 3 years after STEMI showed no difference between patients on β-blockers compared to those who did not take β-blockers. A subgroup analysis of patients with EF ± 40% revealed a significantly lower mortality and fewer major adverse cardiovascular events in the β-blocker group [Figures 2 and 3]. No differences in mortality and MACE were observed in patients with EF > 40%.

Siu et al. [27] assessed the long-term effect of β-blocker therapy among 208 post-MI patients with preserved LV function (EF ≥ 50), negative exercise stress test results, and on ACE inhibitors who were referred to a cardiac rehabilitation program. The study patients were classified according to β-blocker use and monitored prospectively. After a mean follow-up of 58 ± 2 months, patients not on β-blocker therapy had higher incidences of all-cause mortality (P = 0.01), cardiac mortality (P = 0.04) and non-sudden cardiac mortality (P = 0.01). It should be noted that patients on β-blockers in that study were more likely to be treated with statins as well. However, this was a single-center observational study and, given the relatively low risk population, it was a priori underpowered and the findings could therefore be a matter of chance.

Bangalore et al. [28] recently assessed the association of β-blocker use with cardiovascular events in stable patients with a prior history of MI, in those with coronary artery disease without a history of MI, and in those with risk factors only for coronary artery disease. No information was available on the type of MI (STEMI vs. non-STEMI), treatment (conservative, thrombolysis or PCI) or LV function. Following a propensity score matching, no significant difference was found in the primary outcome (composite of cardiovascular death, non-fatal MI or non-fatal stroke) between patients with or without β-blocker therapy. There was also no difference with regard to secondary outcomes or individual components of the primary outcome.

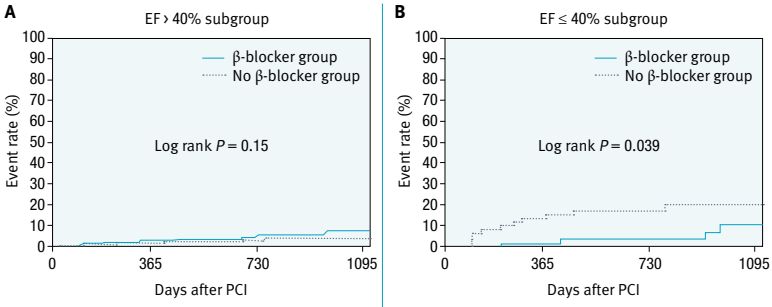
There are, however, several drawbacks to the above-mentioned results. Selection bias for the use of β-blockers is unavoidable in observational studies, and potential confounders, particularly the reasons for failing to prescribe β-blockers, could not be identified and adequately controlled. Moreover, there were no data on types and doses of the β-blockers that had been used, all of which might have affected the clinical outcome.

COMMENT

Although the benefit of long-term treatment with β-blockers after STEMI is well established, data rely mostly on trials predating the advent of modern reperfusion therapy and pharmacotherapy. Many physicians nevertheless remain unconvinced of either a short- or long-term benefit of β-blockade after primary angioplasty because of the lack of evidence that β-blocker treatment following PCI is actually beneficial. Since the utiliza-

MACE = major adverse cardiovascular events
ACE = angiotensin-converting enzyme

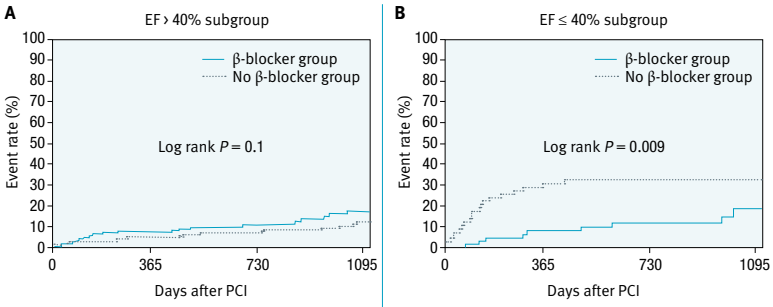
Figure 2. Cumulative incidences of death in STEMI patients from the j-Cypher registry with preserved LVEF **[A]** and in patients with low LVEF **[B]** were compared according to use of β-blockers. From [26] with permission from Elsevier (#3036390789656)



Interval	0	365	730	1095
β-blocker group				
Incidence (%)	0	2.8	5.6	7.6
No. of events	0	6	71	13
No. of patients at risk	217	202	159	77
No β-blocker group				
Incidence (%)	0	1.8	3.3	3.7
No. of events	0	6	10	11
No. of patients at risk	350	317	229	86

Interval	0	365	730	1095
β-blocker group				
Incidence (%)	0	1.7	3.4	10.4
No. of events	0	1	2	4
No. of patients at risk	62	60	40	17
No β-blocker group				
Incidence (%)	0	15.0	17.1	20.1
No. of events	0	9	10	11
No. of patients at risk	63	49	32	18

Figure 3. Cumulative incidences of MACE (all-cause death, recurrent MI, and heart failure hospitalization) in patients with preserved LVEF **[A]** and in patients with low LVEF **[B]** were compared according to use of β blockers. From [26] with permission from Elsevier (#3036390789656)



Interval	0	365	730	1095
β-blocker group				
Incidence (%)	0	7.5	11.4	17.2
No. of events	0	16	23	29
No. of patients at risk	217	192	149	68
No β-blocker group				
Incidence (%)	0	4.7	7.3	11.8
No. of events	0	16	23	29
No. of patients at risk	350	310	222	78

Interval	0	365	730	1095
β-blocker group				
Incidence (%)	0	8.3	12.2	19.1
No. of events	0	5	7	9
No. of patients at risk	62	56	35	17
No β-blocker group				
Incidence (%)	0	31.2	33.3	33.3
No. of events	0	19	20	20
No. of patients at risk	63	40	25	15

tion of β-blockers in primary PCI has not been investigated in contemporary trials, most of the available information is based solely on retrospective analyses of PPCI trials or registries, some of which are not primary STEMI trials [26,28]. Taken together, the above information indicates that current guidelines [1,2] strongly support the use of β-blockers in *all* eligible patients, regardless of the revascularization strategy.

It can be concluded that all patients should receive β-blockers before primary angioplasty and those receiving long-term oral β-blockers before admission should continue to receive them. Pre-procedural β-blocker therapy is of significant benefit for patients who undergo primary PCI. Patients who develop an in-hospital complication, and those who have reduced LV function or a multi-vessel disease derive the greatest benefit from long-term oral therapy. The necessity of β-blockers after successful primary PCI for STEMI in patients with normal EF as well as those with no remaining ischemia and an uncomplicated hospital course will be decided by future prospective clinical trials.

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References

1. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST segment elevation with ST-segment elevation. *Eur Heart J* 2012; 33 (20): 2569-619.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 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. *J Am Coll Cardiol* 2013;61 (4): e78-140.
3. Hjalmarson A, Herlitz J, Holmberg S, et al. The Goteborg metoprolol trial. Effects on mortality and morbidity in acute myocardial infarction. *Circulation* 1983; 67: I26-32.
4. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981; 304: 801-7.
5. β-Bblocker Heart Attack Trial Research Group . A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982; 247: 1707-14.
6. The MIAMI trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomized trial of proanolol in patients with acute myocardial infarction. A randomised placebo-controlled international trial. *Eur Heart J* 1985; 6: 199-226.
7. ISIS-1 Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet* 1986; 2: 57-66.
8. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999; 318: 1730-7.
9. Peter T, Norris RM, Clarke ED, et al. Reduction of enzyme levels by propranolol after acute myocardial infarction. *Circulation* 1978; 57: 1091-5.
10. Roberts R, Croft C, Gold HK, et al. Effect of propranolol on myocardial-infarct size in a randomized blinded multicenter trial. *N Engl J Med* 1984; 311: 218-25.
11. Aupetit JF, Frassati D, Bui-Xuan B, Freysz M, Faucon G, Timour Q. Efficacy of a beta-adrenergic receptor antagonist, propranolol, in preventing ischaemic ventricular fibrillation: dependence on heart rate and ischaemia duration. *Cardiovasc Res* 1998; 37 (3): 646-55.
12. Muller CA, Opie LH, Pineda CA, Peisach M. Bucindolol, a beta blocker, decreased ventricular fibrillation and maintained mechanical function in a pig model of acute myocardial ischemia.*Cardiovasc Drugs Ther* 1992; 6 (3): 233-7.
13. Hjalmarson A. Effects of beta blockade on sudden cardiac death during acute myocardial infarction and the postinfarction period. *Am J Cardiol* 1997; 80: 35-39J.
14. Wolf SC, Sauter G, Preyer M, et al. Influence of nebivolol and metoprolol on inflammatory mediators in human coronary endothelial or smooth muscle cells. Effects on neointima formation after balloon denudation in carotid arteries of rats treated with nebivolol. *Cell Physiol Biochem* 2007; 19: 129-36.
15. Kern MJ, Ganz P, Horowitz JD, et al. Potentiation of coronary vasoconstriction by beta-adrenergic blockade in patients with coronary artery disease. *Circulation* 1983; 67: 1178-85.
16. Viscoli CM, Horwitz RI, Singer BH. Beta-blockers after myocardial infarction: influence of first-year clinical course on long-term effectiveness. *Ann Intern Med* 1993; 118: 99-105.
17. Gheorghiade M, Schultz L, Tilley B, Kao W, Goldstein S. Effects of propranolol in non-Q-wave acute myocardial infarction in the beta blocker heart attack trial. *Am J Cardiol* 1990; 66: 129-33.
18. Report of The Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group. Early treatment of unstable angina in the coronary care unit: a randomized, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both.. *Br Heart J* 1986; 56: 400-13.
19. Goldman L, Sia ST, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. *N Engl J Med* 1988; 319: 152-7.
20. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) II-B Study. *Circulation* 1991; 83: 422-37.
21. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005; 366: 1622-32.
22. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomized trial. *Lancet* 2001; 357: 1385-90.
23. Halkin A, Grines CL, Cox DA, et al. Impact of intravenous beta-blockade before primary angioplasty on survival in patients undergoing mechanical reperfusion therapy for acute myocardial infarction. *J Am Coll Cardiol* 2004; 43: 1780-7.
24. Harjai KJ, Stone GW, Boura J, et al. Effects of prior beta-blocker therapy on clinical outcomes after primary coronary angioplasty for acute myocardial infarction. *Am J Cardiol* 2003; 91: 655-60.
25. Kernis SJ, Harjai KJ, Stone GW, et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? *J Am Coll Cardiol* 2004; 43: 1773-9.
26. Ozasa N, Kimura T, Morimoto T, et al. Lack of effect of oral beta-blocker therapy at discharge on long-term clinical outcomes of ST-segment elevation acute myocardial infarction after primary percutaneous coronary intervention. *Am J Cardiol* 2010; 106: 1225-33.
27. Siu CW, Pong V, Jim MH, et al. Beta-blocker in post-myocardial infarct survivors with preserved left ventricular systolic function. *Pacing Clin Electrophysiol* 2010; 33: 675-80.
28. Bangalore S, Steg G, Deedwania P, et al. Beta-blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012; 308: 1340-9.

"Force without wisdom falls of its own weight"

Horace (born 65 BCE), Roman poet and satirist during the time of Augustus