Chapter 1
Anti-ischemic Therapy

Jose Lopez-Sendón and Esteban López de Sá

Introduction. Definition of Antiischemic Therapy

In a simple way, myocardial ischemia is secondary to a disbalance between oxygen supply in relation to the metabolic demands of the myocardium. Figure 1.1 depicts the principal components of this equation. In acute coronary syndromes plaque rupture and thrombosis play a major role, but other factors that decrease oxygen supply or increase myocardial metabolic demands contribute to ischemia and may be the principal cause of acute ischemia in absence of plaque rupture or coronary artery stenosis.

Reperfusion therapy constitutes the cornerstone for the modern treatment of patients with acute coronary syndromes. Before thrombolysis and percutaneous coronary revascularization, anti-ischemic therapy was the only effective treatment available and beta-blockers, nitrates and calcium channel blockers were routinely used in this clinical setting.

J. Lopez-Sendón, MD, PhD (✉) • E.L. de Sá, MD, FESC
Cardiology Department, Hospital Universitario La Paz,
Instituto de Investigación La Paz IdiPaz,
Paseo de la Castellana 261. Planta 1, Madrid 28046, Spain
e-mail: jlopezsendon@gmail.com

P. Avanzas, P. Clemmensen (eds.), *Pharmacological Treatment of Acute Coronary Syndromes*, Current Cardiovascular Therapy,
DOI 10.1007/978-1-4471-5424-2_1,

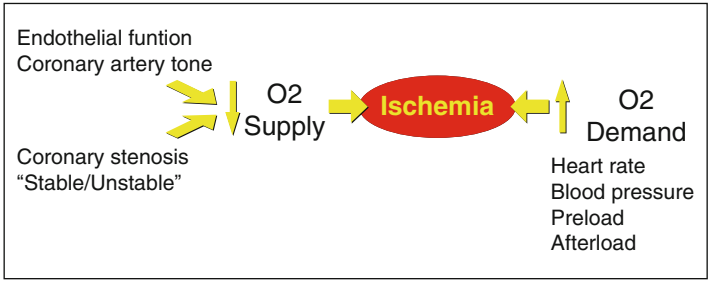


FIGURE 1.1 Myocardial ischemia is the result of multiple possible etiologies that may contribute to an imbalance in myocardial oxygen supply and demand

Today its role is less important; some of the classic drugs provide only a marginal benefit and new drugs with well demonstrated anti-ischemic efficacy in chronic treatments have been tested without much success during the first days of hours of acute coronary syndromes. Nevertheless, ischemia is frequent even after successful modern treatments [1] and anti-ischemic drugs are still needed, in particular for longer treatment strategies after the acute phase.

A significant number of compounds exert an anti-ischemic effect through various mechanism of action, including statins and antithrombotic drugs, but the term of anti-ischemic drugs is reserve for those with a direct anti-ischemic mechanism of action. Table 1.1 summarizes the different categories.

The content of this chapter is intended to provide the available information related to the clinical efficacy of anti-ischemic drugs early after acute coronary syndromes and its practical role in modern treatment strategies (Table 1.2).

Beta-Blockers

β-adrenergic antagonists (beta-blockers) bind selectively to the β-adrenoceptors producing a competitive and reversible antagonism of the effects of β-adrenergic stimuli on various organs. They play a crucial role in a broad spectrum

Table 1.1 Antiischemic drugs and principal mechanisms of action

Drug family	Mechanism of action	Anti-ischemic mechanism
Betablockers	Blockade of B receptors (competitive with chatecolamines)	Heart rate decrease
		Decrease contractility
		Afterload reduction
Nitrates	Nitric Oxide donor	Coronary artery vasodilation
		Preload reduction
Molsidomine	Nitric Oxide donor	Coronary artery vasodilation
		Preload reduction
Nicorandil	Potassium channel (KATP) opener	Free radical protection after reperfusion
	Nitrate-like effect	Nitrate-like effects
Calcium channel blockers	Blockade of voltage-gated calcium channels	Coronary and peripheral arterial vasodilation
	Decrease cellular Ca+ load	Decrease contractility
	Dihidropiridines nitric oxide donors	
Ranolazine	Late Na current blockade	Decreased ischemia induce by Ca+ overload secondary to ischemia
	Decrease cellular Ca+ load	
Ivabradine	If current blockade in sinus node	Pure reduction of heart rate
Trimetazidine	Metabolic	Reduction of free radicals
Other, no direct antiischemic effect	Statins	Endothelia function. Other pleiotropic effects
	Antithrombotics	Improve coronary flow

Table 1.2 Principal indications of anti-ischemic drugs in the early phase (first hours/days) of acute coronary syndromes

Drug family	Clinical settings	Precautions, contraindications
Betablockers oral	All cases w/o contraindications	Hypotension, heart failure, hemodynamic unstability, AV block, Asthma
Nitrates	Hypertension, ongoing non controlled ischemia, heart failure	Patients with hypotension
Molsidomine	Acute setting: None	
Calcium channel blockers	Acute setting: None Can be used later if myocardial ischemia, hypertension	Hypotension, heart failure, hemodynamic unstability, AV block, heart failure
Ranolazine	Acute setting: None Can be used later if myocardial ischemia	
Ivabradine	Acute setting: None Can be used later if heart rate >60 beats/minute	
Trimetazidine	Acute setting: None	

of cardiovascular diseases and have demonstrated clinical benefit in patients with unstable angina and acute myocardial infarction [2].

Mechanism of Action

The mechanisms of action of beta-blockers are diverse, not yet completely understood and probably with important differences between agents. The prevention of the cardiotoxic effects of catecholamines plays a central role [3]. Beta-blockers decrease myocardial oxygen demand by reducing

heart rate, cardiac contractility, and systolic blood pressure [4]. These are the main anti-ischemic effects. In addition, prolongation of diastole caused by a reduction in heart rate may increase myocardial perfusion. Other beneficial actions include an antihypertensive effect associated with a decrease in cardiac output, inhibition of the release of renin and production of angiotensin II, blockade of presynaptic β2-adrenoceptors that increase the release of norepinephrine from sympathetic nerve terminals. Important in acute ischemia, beta-blockers exert a very effective antiarrhythmic action that may explain the reduction in cardiac death observed in patients of acute coronary syndromes and heart failure. Other more complex mechanisms probably are not relevant in the clinical setting of acute coronary syndromes.

Clinical Settings. Acute Myocardial Infarction

Beta-blockers limit infarct size, reduce life-threatening arrhythmias, relieve pain and reduce mortality including sudden death [2, 5–11]. Two large trials were particularly relevant to guide the use of beta-blockers during the first hours of AMI. In the First International Study of Infarct Survival (ISIS-1) trial [8] patients within 12 h of evolution were randomised to receive iv atenolol followed by oral administration for 7 days, or conventional treatment, revealing a significant reduction in mortality at 7 days (3.7 % vs 4.6 %; equivalent to 6 lives saved per 1,000 treated) (Fig. 1.2). The benefit was mainly due to a reduction in heart rupture and was evident by the end of day 1 and sustained at 1 month and 1 year. In the other large study, the Metoprolol in Myocardial Infarction (MIAMI) [9], iv metoprolol followed by oral administration did not significantly reduce 15-day mortality as compared to placebo (4.3–4.9 % (ns)). A metaanalysis of 28 early trials of iv beta-blockers [11] revealed an absolute reduction of short-term mortality from 4.3 to 3.7 % (7 lives saved/1,000 patients treated). This significant albeit small benefit was demonstrated before the reperfusion era. Similar

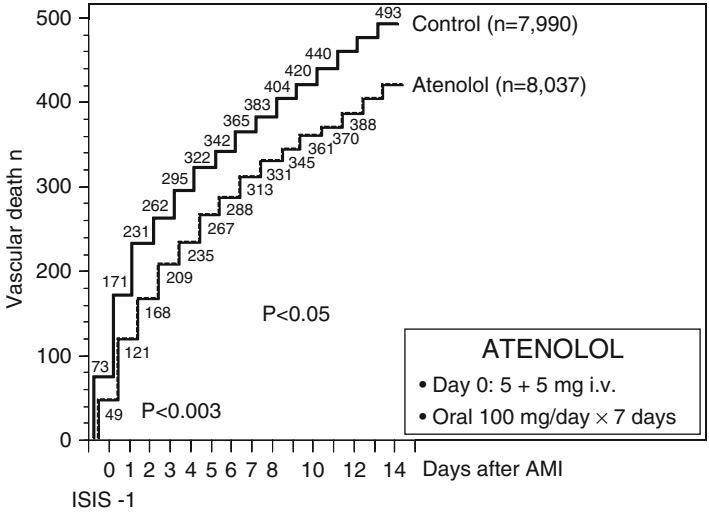


FIGURE 1.2 Cumulative vascular mortality in the groups of patients allocated to atenolol and placebo in the ISIS-1 trial (Reprinted with permission from ISIS-1 (First International Study of Infarct Survival) Collaborative Group [8])

findings were reported in a more recent metaanalysis of 52 trials, most of them including a small number of patients [12].

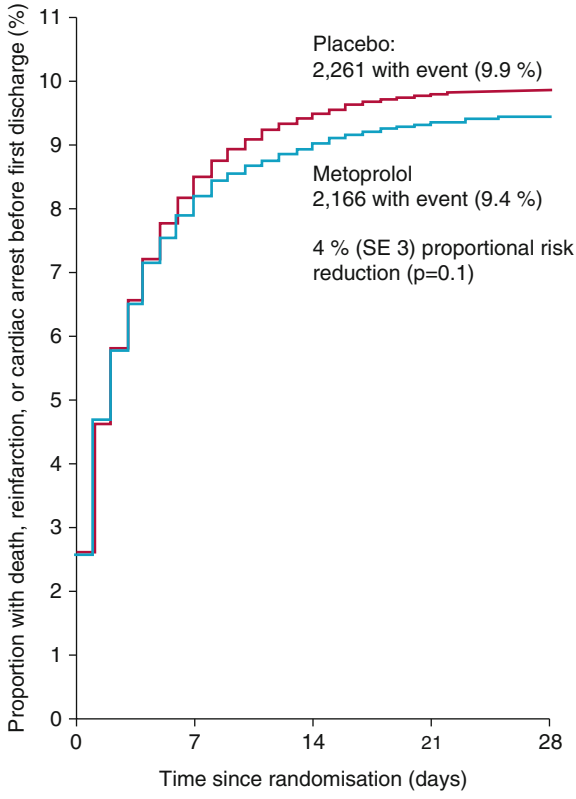
Three trials of randomised iv beta-blockade were conducted after the widespread use of reperfusion therapy in AMI [13–15], but the number of events was too small to establish clear conclusions. In the second Thrombolysis in Myocardial Infarction (TIMI-II) trial [13], thrombolysed patients were randomly assigned to early iv and oral metoprolol versus oral administration after day 6. Reinfarction and recurrent ischaemia were less frequent in the early beta-blocker group and when treatment was administered within 2 h of symptom onset, there was a reduction of the composite endpoint of death or reinfarction.

The COMMIT trial [15] Metoprolol (15 mg iv, then 200 mg oral daily) 45,000 Chinese patients with suspected acute STEMI within 24 h of evolution were randomly assigned to

metoprolol (15 mg iv, then 200 mg oral daily) or placebo. About half received thrombolytic therapy. Exclusion criteria were shock at admission, systolic blood pressure <100 mmHg, heart rate <50 bpm and AV block. Mean treatment and follow up was 16 days. The study failed to demonstrate a reduction of total mortality in patients receiving metoprolol (Fig. 1.3), the benefit of metoprolol was limited to a reduction in arrhythmic dead (1.7 % vs 2.2 %; $p < 0.01$) and re-infarction (2 % vs 2.5 %; $p < 0.002$), somehow counterbalanced by an increase in mortality secondary to cardiogenic shock. The overall effect on death, reinfarction, cardiac arrest, or shock was significantly adverse during days 0–1 and significantly beneficial thereafter. There was substantial net hazard in haemodynamically unstable patients, and moderate net benefit in those who were relatively stable. The results of this somehow polemic trial, strongly suggest that intravenous beta-blockers should not be routinely used in patients with acute myocardial infarction in particular if the present heart failure or hemodynamic instability.

A global metaanalysis including these modern trials still provide evidence for benefit (Fig. 1.4), although some restrictions have to be considered and the metaanalysis includes completely different trials belonging to different times [15].

Registries offer a practical insight for the use of beta-blockers in the reperfusion era. Data from the US National Registry of Myocardial Infarction 2 [16] showed that immediate beta-blocker administration in patients with AMI treated with t-PA reduces the occurrence of intracranial haemorrhage, although this benefit is small (0.7 % and 1.0 %; 3 patients/1,000 treated). However, a post-hoc analysis of the first Global utilization of streptokinase and t-PA for occluded coronary arteries (GUSTO-I) trial and a systematic review of the available experience do not support the routine, early, *intravenous* use of beta-blockers [17, 18], at least when thrombolytic treatment or primary percutaneous intervention is performed. New data from the PAMI (Primary Angioplasty in AMI) Stent-PAMI, Air-PAMI and CADILLAC (Controlled Abciximab and Device



Days	0–6	7–13	14–20	21–28
Number of events				
Metoprolol	1,796	244	93	33
Placebo	1,862	291	83	25

FIGURE 1.3 Death, myocardial infarction or cardiac arrest before hospital discharge in the COMMIT trial. No statistical differences were observed between metoprolol and placebo (Reprinted with permission from COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group [15])

Investigation to Lower Late Angioplasty Complications) trials seem to demonstrate a reduction in mortality when beta-blockers are used before primary percutaneous interventions [19–21].

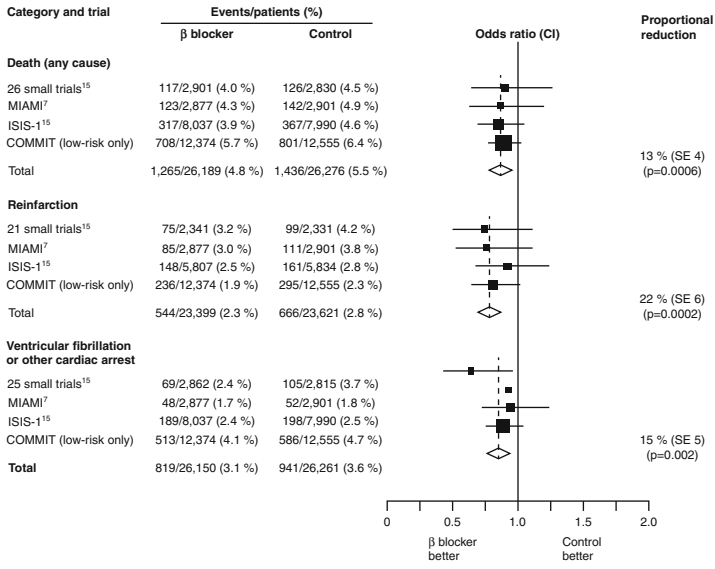


FIGURE 1.4 Metaanalysis of betablockers in patients with acute myocardial infarction, demonstrating a benefit in outcomes: mortality, myocardial infarction and ventricular fibrillation or other cardiac arrest (Reprinted with permission from COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group [15])

In 13,110 patients with STEMI who received beta-blockers during the index hospitalization in the GRACE registry (emery) intravenous beta-blocker use (adjusted odds ratio 1.46, 95 % CI 1.31–1.64, $P \leq 0.0001$) and delayed beta-blocker use (after 1st 24 h) (adjusted odds ratio 1.35, 95 % CI 1.19–1.54, $P \leq 0.0001$) were associated with a higher composite outcome of death, cardiogenic shock, sustained ventricular fibrillation/ventricular tachycardia, and new heart failure when compared to early (1st 24 h) oral beta-blocker use. There was a reduction in mortality in patients who had delayed beta-blocker administration (adjusted odds ratio 0.56, 95 % CI 0.41–0.78, $P \leq 0.001$) [22].

This data suggests that in acute STEMI early intravenous beta-blockers and delayed beta-blockers were associated with worse short-term outcomes compared with early oral administration.

Non ST Segment Elevation Acute Coronary Syndromes

There are few randomised studies with beta-blockers in patients with unstable angina and non Q wave myocardial infarction [23–25], and the new non-ST elevation ACS terminology makes the analysis of possible effect even more difficult. Henceforth, the recommendations are based on small studies in unstable angina as well as in the evidence in acute ST elevation myocardial infarction and stable patients with ischaemia and previous myocardial infarction. In fact, there are few studies in patients with unstable angina comparing beta-blockers with placebo A meta-analysis suggested that beta-blocker treatment was associated with a 13 % relative reduction in risk of progression to AMI [26]. A retrospective analysis from the Cooperative Cardiovascular Project [27] indicates that the relative risk of death was lower in patients with non Q wave myocardial infarction receiving beta-blockers. Pooled data from 2,894 patients with acute coronary syndromes included in five randomized, controlled trials of abciximab during coronary intervention showed a reduction of 30 day and 60 day mortality associated with the use of beta-blockers [28]. There is no evidence that any specific beta-blocking agent is more effective in producing beneficial effects in unstable angina and oral therapy should be aimed to achieving a target heart rate between 50 and 60 beats per minute.

In a cohort of 7,106 patients with NSTEMI from the GRACE registry [29], beta-blocker therapy was initiated within the first 24 h in 76 % of patients with NSTEMI (79 % with Killip class I vs 62 % with class II/III; $p < 0.001$). Failure to initiate beta-blockers within the first 24 h was associated with lower rates of subsequent beta-blocker therapy and other evidence-based therapies. Early beta-blocker therapy was correlated with lower hospital mortality for NSTEMI patients (OR 0.58, 95 % CI 0.42–0.81) and for those with Killip class II/III (OR 0.39, 95 % CI 0.23–0.68) with a trend toward lower mortality in the Killip class I group

(OR 0.77, 95 % CI 0.49–1.21). At 6 months post discharge, early BB use was associated with lower mortality in NSTEMI patients (OR 0.75, 95 % CI 0.56–0.997) with a trend toward lower mortality in patients with Killip class I or II/III.

Beta-blockers can increase coronary artery tone and are contraindicated in vasospastic angina without obstructive lesions [30].

Adverse Events

In general, β-adrenergic inhibitors are well tolerated, but serious side-effects may occur, especially when these agents are used in large doses [2]. Beta-blockers reduce heart rate and may cause extremebradycardia and AV block. Beta-blockers can also increase the coronary vasomotor tone, in part because of unopposed α-adrenergic mediated vasoconstriction. Beta-blockers can lead to a life-threatening increase in airway resistance and are contraindicated in patients with asthmaor bronchospastic chronic obstructive pulmonary disease. In some patients with chronic obstructive pulmonary disease, the potential benefit of using beta-blockers may outweigh the risk of worsening pulmonary function.

Contraindications

The contraindications to initiate beta-blocker treatment include asthma, symptomatic hypotension or bradycardia and severe decompensated heart failure. Contraindications may be relative, in patients in whom the benefit of therapy may outweigh the risk of untoward effects. Chronic obstructive lung disease without bronchospastic activity and peripheral vascular disease are not considered as absolute contraindications and high risk patients may obtain a significant benefit from this therapy [27, 28]. Diabetes or intermittent lower limb claudication are not absolute contraindications for beta-blockers use [2]. Heart failure during the acute setting of myocardial infarction is a formal contraindication for the use

of intravenous beta-blockers. However, oral beta-blockers can be safely administered in patients with heart failure when the patient is stable and without need of intravenous inotropic support [31].

Drug Interactions

Beta-blockers may show pharmacokinetic and pharmacodynamic interactions with other drugs [2]. Aluminium salts, cholestyramine, and colestipol may decrease the absorption of beta-blockers. Alcohol, phenytoin, rifampicin, and phenobarbital, as well as smoking, induce hepatic biotransformation enzymes and decrease plasma concentrations and elimination half-lives of lypophilic beta-blockers. Cimetidine and hydralazine may increase the bioavailability of propranolol and metoprolol by reducing hepatic blood flow. Caution should be exercised in patients who are taking verapamil, diltiazem or various antiarrhythmic agents, which may depress sinus-node function or AV conduction. Additive effects on blood pressure between beta-blockers antagonists and other antihypertensive agents are often observed. Indometacin and other nonsteroidal anti-inflammatory drugs antagonize the antihypertensive effects of beta-blockers.

Dosing of Beta-Blockers

Appropriate dosing of beta-blockers varies with the clinical characteristics of the patient and the selected beta-blocker. Atenolol, metoprolol and carvedilol are the beta-blockers with the largest experience in the setting of acute coronary syndromes.

Calcium Channel Blockers

Calcium Channel Blockers (CHB) exert an anti-ischaemic effect through several mechanisms. The reduce afterload as the decrease blood pressure and contractility, have a

vasodilatory effect in the coronary arteries and non-hydropiridines reduce heart rate [32]. Clinical trials with verapamil, diltiazem and nifedipine failed to demonstrate a consistent significant benefit in patients with acute coronary syndromes in studies conducted in the early 1980s with low use of antiaggregants, beta-blockers, statins, and revascularization. In the DAVIT-1 trial, treatment was started with 0.1 mg/kg verapamil i.v. and 120 mg/day orally on admission followed by 120 mg three times daily, or matched placebo. Mortality and reinfarction rates were similar in both groups of treatment during hospitalization and after 6 and 12-month follow-up of continuous treatment [33] (Fig. 1.5). In the Multicenter Diltiazem Reinfarction Study, conducted in 576 patients recovering from acute non-Q-wave MI treated with either diltiazem or placebo, treatment was initiated 24–72 h after the onset of MI and continued for 14 days. Active treatment did not modify total mortality, but reduced the early reinfarction rate compared with placebo (9.3 % vs 5.2 %, $P < 0.03$) [34].

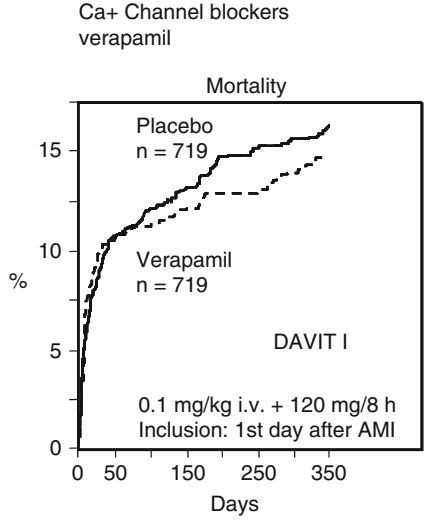


Figure 1.5 Mortality rate was similar in the groups treated with verapamil and placebo in the DAVIT-1 trial in patients with acute myocardial infarction (Reprinted with permission from The Danish Study Group on Verapamil in Myocardial Infarction [33])

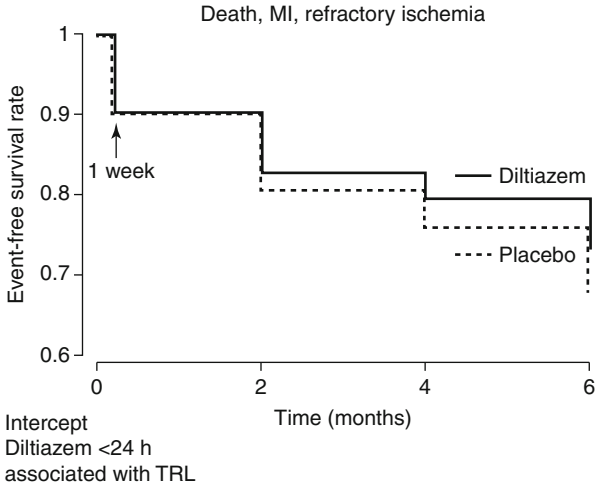


FIGURE 1.6 Mortality, myocardial infarction and refractory ischemia in the INTERCEPT trial, comparing diltiacem against placebo in patients with acute myocardial infarction (Reprinted with permission from Boden et al. [35])

In another prospective, randomized, double-blind, sequential trial in 874 patients with acute myocardial infarction, but without congestive heart failure, who first received thrombolytic agents (INTERCEPT trial), patients received either oral diltiazem or placebo, initiated within 36–96 h of infarct onset, and given for up to 6 months. Diltiazem did not reduce the cumulative occurrence of cardiac death, nonfatal reinfarction, or refractory ischemia during a 6-month follow-up (Fig. 1.6), but the need for revascularization was lower in the diltiazem group [35]. There is no information related to the possible benefit of CCB in patients with ACS treated according to contemporary strategies.

Hydropiridines have been also tested in acute coronary syndromes, and no benefit could be demonstrated in any of the trials. The NAMIS study [36] found that in patients with ischemic pain of >45 min duration nifedipine therapy (20 mg orally every 4 h for 14 days) did not prevent progression of

threatened myocardial infarction to the acute event or limit infarct size in patients who experienced infarction. Among the 171 patients randomly assigned to drug or placebo, 6 months mortality did not differ between both groups (8.5 % for placebo vs 10.1 % for nifedipine), but mortality in the 2 weeks after randomization was significantly higher for nifedipine-treated patients (0 % for placebo vs 7 % for nifedipine, $P = 0.018$). The results indicate that nifedipine did not reduce the likelihood of progression from threatened myocardial infarction (TMI) to acute MI. In addition, nifedipine did not limit infarct size in those patients with TMI in whom infarction evolved or in patients in whom infarction was already in progress at the time of randomization. The reason for the lack of beneficial effect may have been the detrimental effects of the reduction in coronary blood flow caused by nifedipine-induced hypotension that may outweighed the beneficial effects of a decrease in afterload produced by the drug.

Accordingly, there is no evidence to recommend the routine use of calcium channel blockers as anti-ischemic therapy in patients with acute coronary syndromes.

Nitrates

Nitrates have been the all-time anti-ischemic agents in patients with acute coronary syndromes, chronic angina and secondary prevention. They quickly relieve acute episodes of angina and sublingual administration of short acting nitrates have been and still are the recommended medication to jugulate acute episodes of angina. In a small percentage of patients, nitroglycerin can open an otherwise occluded coronary artery during an episode of chest pain (Fig. 1.7).

Nitrates produce nonspecific smooth muscle relaxation through direct tissue action. This effect is independent of any known neurotransmitter [37]. At the level of the smooth muscle fiber, nitrates facilitate formation of nitric oxide (NO) that stimulates guanalyl cyclase activity, and increases the intracellular concentration of cGMP. CGMP decreases the

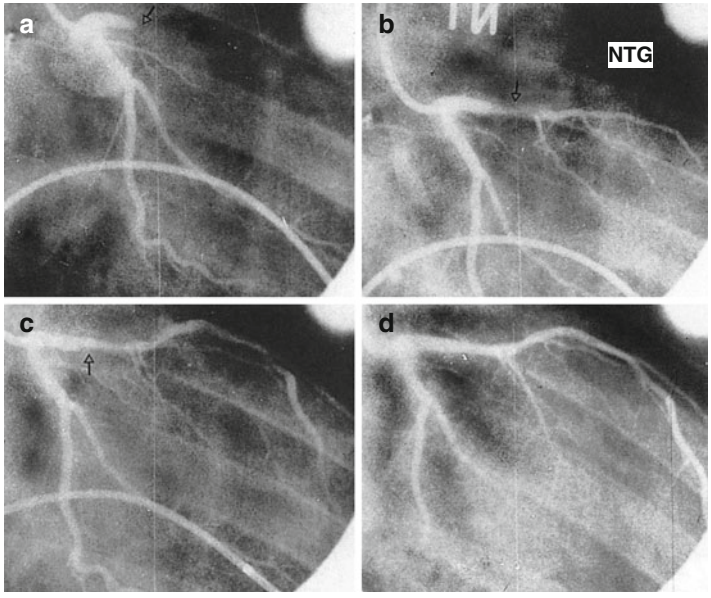


FIGURE 1.7 Coronary angiography in a patient with acute myocardial infarction. (**a**) Complete proximal occlusion of the left anterior descending coronary artery. (**b**) Restoration of flow after administration of nitroglycerine. (**c**, **d**) Final results after coronary angioplasty

intracellular concentration of free calcium, thereby causing smooth-muscle relaxation. Nitrates may combine with endogenous sulfhydryl groups, forming S-nitrositols (R-SNO) that subsequently converts to NO. Under physiologic conditions, the endothelium releases NO that acts as an endogenous nitrate, producing coronary vasodilation. In patients with ischemic heart disease, in whom the coronary endothelium is damaged, nitrates induce the formation of NO in smooth muscle cells, producing vasodilatation. Nitrates, present tachyfilaxia, and its effect disappears with time [38].

The primary action of nitrates is vasodilation, which is attributable primarily to nitrate-induced relaxation of vascular smooth muscle in veins, arteries, and arterioles. The metabolic

conversion of organic nitrates to nitric oxide (NO) at or near the plasma membrane of the vascular smooth muscle cell represents the cellular basis for the vasodilatory action of these compounds. Believed to be an endothelium-derived relaxing factor (EDRF), NO is an important endogenous modulator of vascular tone. Nitrate administration has been viewed as a means of providing an exogenous source of NO that may help replenish or restore the actions of EDRF, which are usually impaired in patients with coronary artery atherosclerosis.

The reduction in right and left ventricular preload resulting from peripheral vasodilation, particularly in the splanchnic and mesenteric circulations, combined with afterload reduction resulting from arterial vasodilation, decreases cardiac work and lowers myocardial oxygen requirements. As a consequence, the ratio of myocardial oxygen demand to myocardial oxygen supply improves, and myocardial ischemia is alleviated. Because of their hemodynamic profile, nitrates are particularly useful in patients with impaired LV systolic function or heart failure. Additionally, both direct vasodilator effect of nitrates on the coronary bed and drug-induced prevention of episodic coronary artery vasoconstriction can increase global and regional myocardial blood flow, improving the subendocardial-epicardial blood flow ratio. Enlargement of obstructive atherosclerotic lesions containing intact vascular smooth muscle can increase the caliber of some stenoses, improving coronary flow. Nitrates also have been shown to dilate coronary collateral vessels, reverse vasoconstriction of small coronary arteries distal to a coronary obstruction, and reduce platelet aggregation.

Clinical Benefit

Few earlier trials prospectively randomized patients with acute coronary syndromes to explore the clinical efficacy of nitrates and most information is focusing on infarct size, enzymatic release and other surrogates for clinical efficacy; besides, the number of patients we were very small to draw conclusions.

In one of such trials, Judgutt et al. [39] 310 patients were randomly allocated to i.v. niroglycerin and control groups. Nitroglycerin infusion was titrated to lower mean blood pressure by 10 % in normotensive and 30 % in hypertensive patients, but not below 80 mmHg, and was maintained for 39 h.

Compared with controls, nitroglycerin decreased creatine kinase infarct size. Other indexes of infarct size (i.e. left ventricular asynergy, left ventricular ejection fraction, and Killip class score) also improved. Infarct-related major complications were less frequent in the NG than the control groups: infarct expansion syndrome, left ventricular thrombi thrombus, cardiogenic shock and infarct extension. Mortality was less in NG than in control groups in-hospital (14 % vs 26 %, $p < 0.01$), at 3 months (16 % vs 28 %, $p < 0.025$) and 12 months (21 % vs 31 %, $p < 0.05$), but this advantage was only found in patients with anterior Q wave infarction. Greater benefit on infarct size occurs with early timing (<4 h) and target mean blood pressure ≥80 mmHg.

These fantastic results prompted the organization of several megatrials in order to ascertain that nitrates should be routinely used in all patients with acute coronary syndromes. None demonstrated any relevant clinical benefit.

The GISSI-3 study was a multicentre randomized clinical trial to assess the efficacy of lisinopril, transdermal glyceryl trinitrate, and their combination in improving survival and ventricular function after acute myocardial infarction [40]. The GISSI-3 trial randomly assigned 19,394 patients within 24 h of symptom onset to a 24-h infusion of nitroglycerin (beginning within 24 h of onset of pain), followed by topical nitroglycerin (10 mg daily) for 6 week (with patch removed at bedtime, allowing a 10-h nitrate-free interval to avoid tolerance), or control. Approximately 50 % of patients in the control group received nitrates on the first day or two at the discretion of their physician, a major mistake in the design of the trial. There was an insignificant, and certainly non clinical relevant, reduction in mortality at 6 weeks in the group randomly assigned to nitrate therapy alone, compared with the control group (6.52 % vs 6.92 %, respectively) (Fig. 1.8).

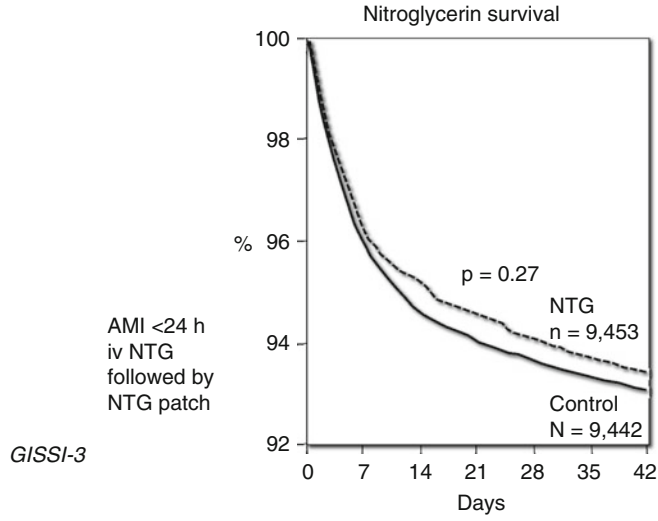


FIGURE 1.8 Survival curves in patients with acute myocardial infarction treated with nitroglycerine or placebo in the GISSI-3 trial (Reprinted with permission from Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico [40])

There were no significant differences between nitroglycerin-allocated and control patients in rates of reinfarction, revascularization procedures, persistent hypotension or renal dysfunction. The nitrate group had a lower rate of reinfarction angina ($P = 0.03$) and cardiogenic shock ($P = 0.009$). However, there was a significant excess of stroke rate in the nitrate group compared with controls ($P = 0.027$).

Another megatrial was organized to demonstrate that 5-isosorbide mononitrate, and oral nitrate with somehow a prolonged action for several hours. The purpose of the ISIS 4 study [41] was the reliable assessment of the effects on mortality and major morbidity of the addition of three widely used treatments in patients with definite or suspected acute myocardial infarction. 58,050 patients were randomized in a "$2 \times 2 \times 2$ factorial" design. The treatment comparisons were: (1) 1 month of oral captopril versus matching placebo; (2) 1

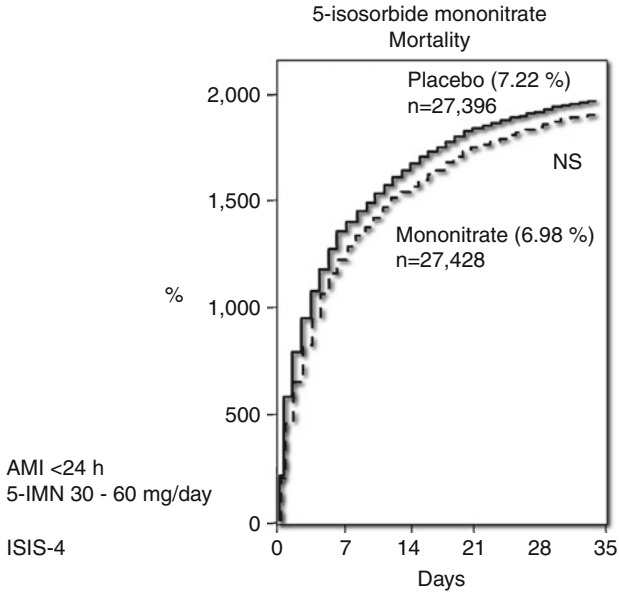


FIGURE 1.9 Mortality in patients with acute myocardial infarction treated with 5-isosorbide monotitrate or placebo in the ISIS 4 trial (Reprinted with permission from ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group [41])

month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg once daily) versus matching placebo, and (3) 24 h intravenous magnesium sulphate versus open control. Patients entering in the study up to 24 h (median 8 h) after the onset of suspected acute MI. At 5-weeks follow-up, there were 2,129 (7.34 %) deaths recordedamong 29,018 mononitrate-allocated patients compared with 2,190 (7.54 %) among 29,032 patients allocated matching placebo (P = 0.3) (Fig. 1.9). Follow-up to 1 year did not indicate any further divergence or convergence of the survival curves following 1 month of oral mononitrate. There were not differences in the incidence of reinfarction, post infarction angina or heart failure, but severe hypotension requiring termination of study treatment was more frequent in the nitrate group (8.1 % mononitrate vs 6.7 % placebo,

P < 0.0001). The high number of patent included in the trial permitted to explore different subgroups, but the study was consistently neutral in all.

A meta-analysis including the GISSI 3 and ISIS 4 data in addition of 20 small trial (11 by intravenous and by 9 oral administration) involving over 81,000 patients indicates that the role of nitrates in the treatment of acute coronary syndromes is marginal [41] and its use should be restricted to control hypertension, pulmonary congestion or refractory ischemia.

Molsidomine

In the believe that nitric oxide donors were potentially highly beneficial to control acute or chronic ischemia, other compounds were investigated in this clinical settings. In the ESPRIM trial, molsidomine, with and active metabolite, linsidomine, a nitric oxide donor was compared with placebo in a large-scale trial including 4,017 patients with acute myocardial infarction. Patients without signs of overt heart failure (Killip III/IV) were randomly assigned in a double-blind design within 24 h of symptom onset to receive molsidomine 1 mg/h intravenously for 48 h, followed by 16 mg molsidomine by mouth daily for 12 days, or an identical placebo [42]. The molsidomine and placebo groups showed similar all-cause 35-day mortality (8.4 % vs 8.8 %, p = 0.66), Similarly, no differences were found for long-term mortality (mean follow-up 13 months; 14.7 % vs 14.2 %, p = 0.67) (Fig. 1.10). The two groups showed similar frequencies of major and minor adverse events; only headache was significantly more common in the molsidomine group. It is still not clear whether nitric oxide donors can improve survival in higher-risk myocardial infarction patients.

Nicorandil

Adenosine triphosphate sensitive potassium channel openers (KATP) exert cardioprotectiveeffects in ischemic myocardium mimicking ischemic preconditioning. Nicorandil is

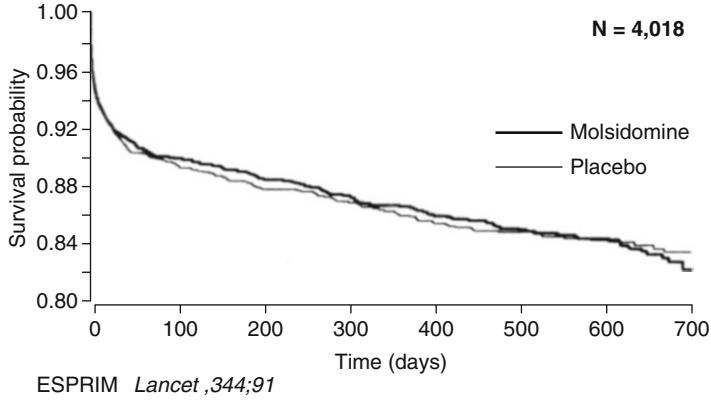


Figure 1.10 Survival curves for patients allocated to molsidomine or placebo in the ESPRIM trial (Reprinted with permission from European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group [42])

a KATP channel opener with additional properties similar to those of nitrate nitrates [43]. Several studies have been conducted in patients with acute myocardial infarction with and without reperfusion, trying to demonstrate some protective effect of nicorandil. The largest study, the J-MIND [44] included 545 patients with acute infarction undergoing reperfusion and failed to demonstrate benefit on the primary endpoint (infarct size measured by creatin kinase levels and Leith ventricular function evaluated with ventricular agiography).

In a meta-analysis of 17 studies including over 1,500 patients [45] nicorandil treatment reduced the incidence of TIMI flow grade ≤2 in the culprit artery, was associated with greater LVEF than placebo and no beneficial effect was observed on the peak creatine kinase value.

In conclusion, nicorandil treatment adjunctive to reperfusion therapy has some beneficial effects on microvascular function and on functional recovery after AMI but there is no clinical evidence of benefit and hence no indication in acute coronary syndromes.

Ranolazine

Ranolazine, a piperazine derivative, selectively inhibits the late inward sodium current (late I_{Na}) [46], a pathological current which occurs in ischemic conditions. Blocking late I_{Na} attenuates ischemia related myocardial sodium overload and, subsequently, intracellular calcium overload, a mediator of further myocardial ischemia. It is thought that the reduction in diastolic calcium overload improves myocardial relaxation and reduces left ventricular diastolic stiffness, which in turn may enhance myocardial perfusion and reduce subendocardial oxygen demand. Ranolazine produces anti-ischemic effects without depressing hemodynamic function while exerting minimal effects on heart rate and blood pressure. Ranolazine is approved for the treatment of chronic angina.

The MERLIN trial was designed to explore the efficacy of ranolazine against placebo in patients with acute coronary syndromes. The trial included 6,560 patients within 48 h of ischemic symptoms [47]. Ranolazine was initiated intravenously and followed by oral ranolazine extended-release 1,000 mg twice daily, or matching placebo. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, or recurrent ischemia through the end of study. And was not significantly different in the ranolazine and placebo groups (21.8 % vs 23.5 %, $p=0.11$). Recurrent ischemia was reduced in the ranolazine group (13.9 %) vs 16.1 %, $p<0.03$ and in patients with chronic angina reduced the composite outcome of cardiovascular death and myocardial infarction [48]. The trial concluded that the effect was not enough to recommend ranolazine in acute coronary syndromes but the trial provided support for the safety and efficacy of ranolazine to treat chronic stable angina.

Trimetazidine

Trimetazidine is an antianginal agent that has no negative inotropic or vasodilator properties. Although it is thought to have direct cytoprotective actions on the myocardium, the

mechanisms by which this occurs are not completely defined but probably it shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial enzymes [49].

The EMIP–FR (European Myocardial Infarction Project – Free Radicals) was a prospective, double-blind, European multicentre trial compare the effect of trimetazidine versus placebo administered to 19,725 patients during the acute phase of myocardial infarction (within the first 24 h) on long and short-term mortality [50]. Stratification was according to thrombolytic therapy (56 %) or not (44 %). An intravenous bolus injection of trimetazidine (40 mg) was given just before or simultaneously with thrombolysis, followed by continuous infusion (60 mg/24 h) for 48 h. Overall, no difference was found between trimetazidine and placebo for the main end-point, short-term (35-day) mortality, (P = 0.98) in an intention-to-treat analysis. This was the result of opposing trends in the two strata. Thrombolysed patients showed a tendency towards more short-term deaths with trimetazidine, compared to placebo (11.3 %, vs 10.5 %, p = 0.15) and non thrombolysed patients the converse (trimetazidine: 14.0 %, placebo: 15.1 %, p = 0.14). For non thrombolysed patients, in a per-protocol analysis the beneficial effect of trimetazidine became statistically significant (trimetazidine: 13.3 %, placebo: 15.1 %, P = 0.027).

In conclusion, trimetazidine does not reduce mortality in patients undergoing thrombolytic therapy; however, it might have some beneficial effect fornon thrombolysed patients.

If Channel Blockers. Ivabradine

Heart rate plays a major role in some major factors related with the pathophysiology of ACS. Increased heart rate is associated with endothelial dysfunction, plaque instability and ruptureand a decreased threshold for ventricular fibrillation. A high heart rate in patients with ACS increases cardiac work and myocardial oxygen consumption, and reduces

diastolic myocardial perfusion time. This can produce an imbalance between myocardial oxygen demand and supply, contributing to ischemia in patients with ACS [51]. In addition, after an acute complete coronary artery occlusion, collateral circulation plays a crucial role and is related to prognosis and collaterals are much more frequently visible on angiography in presence lower hear rates.

In the contemporary Global Registry of Acute Coronary Events (GRACE), including patients with ST-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina, heart rate was an independent prognostic factor in an elaborated model, with an attributable risk for in-hospital and post-discharge mortality of 5–10 % for each 10 bpm increase in heart rate [52]. Similar findings were observed in other trials and registries [53]. Despite of this evidence, A relatively recent observational study demonstrated that only a minority of post-ACS patients (5.3 %) treated according to current guidelines reached the recommended level of heart rate during their hospital stay [54].

Some of the benefit obtained with beta-blockers in patients with ACS may be derived from a reduction in heart rate, with a direct relationship between the obtained heart rate reduction and the reduction in infarct size, reinfarction, and clinical outcomes including mortality [55]. This relationship has not been demonstrated with calcium channel blockers.

Ivabradine, the only available selective inhibitor of the I_f current, reduces heart rate without affecting cardiac contractility or blood pressure. In experimental models, ivabradine reduced oxygen consumption, increased myocardial blood flow, improved endothelial and myocardial function, and reduced infarct size [55].

In the VIV*If*Y trial intravenous ivabradine reduce heart rate and left ventricular volume as compared with placebo in patients with STEMI and primary PCI. This pilot trial showed that the use of the drug was safe and opens an opportunity to explore a new family drugs for the treatment of ischemia in patients with acute coronary syndromes.

Conclusions

Anti-ischemic agents still play a role in acute coronary syndromes in the reperfusion era. However, only betablockers can be recommended as a routine treatment in absence of contraindications. Beta-blockers should be started *per os* as soon as possible and its intravenous administration should be reserved for special cases such as patients with severe arrhythmias. Other antiischemic therapies should only be considered in special situations and for the treatment of myocardial ischemia after the acute episode.

References

1. Arnold SV, Morrow D, Ley Y, Cohen DL, Mahoney EM, Braunwald E, Cahn PS. Economic impact of angina after an acute coronary syndrome: insights from the MERLIN-TIMI 36 trial. Circ Cardiovasc Qual Outcomes. 2009;2:344–53.
2. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kiekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J. 2004;25:1454–70.
3. Waagstein F. Beta-blockers in congestive heart failure: the evolution of a new treatment concept-mechanism of action and clinical implications. J Clin Basic Cardiol. 2002;5:215–23.
4. Frishman WH. Multifactorial actions of beta-adrenergic-blocking drugs in ischemic heart disease: current concepts. Circulation. 1983;67(Suppl I):I-11–8.
5. Hjalmarson Å, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet. 1981;ii:823–7.
6. Richterova A, Herlitz J, Holmberg S, et al. The göteborg metoprolol trial in acute myocardial infaction. Effects on chest pain. Am J Cardiol. 1984;53:32D–6.
7. Norris RM, Brown MA, Clarke ED, et al. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. Lancet. 1984;2:883–6.
8. ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16027 cases of suspected acute myocardial infarction: ISIS-1. Lancet. 1986;II:57–66.
9. The MIAMI Trial Research Group: Metoprolol in acute myocardial infarction (MIAMI). Am J Cardiol. 1985;56:1G–57.

10. Ryden L, Ariniego R, Arnman K, et al. A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachyarrhythmias. N Engl J Med. 1983;308:614–8.
11. Yusuf S, Lessem J, Pet J, et al. Primary and secondary prevention of myocardial infarction and strokes. An update of randomly allocated controlled trials. J Hypertens. 1993;11 Suppl 4:S61–73.
12. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction. Systematic review and meta regression analysis. BMJ. 1999;318:1730–7.
13. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction (TIMI) IIB study. Circulation. 1991;83:422–37.
14. Van de Werf F, Janssens L, Brzostek T, et al. Short term effect of early intravenous treatment with beta-adrenergic blocking agents or a specific bradycardia agent in patients with acute myocardial infarction receiving thrombolytic therapy. J Am Coll Cardiol. 1993;2:407–16.
15. 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;366:1622–32.
16. Barron HV, Rundle AC, Gore JM, et al., for the Participants in the national registry of myocardial infarction-2. Intracranial hemorrhage rates and effect of immediate beta-blocker use in patients with acute myocardial infarction treated with tissue plasminogen activator. Am J Cardiol. 2000;85:294–8.
17. Pfisterer M, Cox JL, Granger CG, et al. Atenolol use and clinical outcomes after thrombolysis for acute myocardial infarction. The GUSTO-I experience. Global utilization of streptokinase and TPA (alteplase) for occluded coronary arteries. J Am Coll Cardiol. 1998;32:634–40.
18. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC guidelines for the management of acutemyocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33:2569–619.
19. 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.
20. Halkin A, Nikolsky E, Aymong E, et al. The survival benefit of periprocedural beta-blockers in patients with acute myocardial infarction undergoing primary angioplasty is determined by use of these drugs before admission. Am J Cardiol. 2003;92(Suppl L):228L.
21. Kernis SJ, Arguya KJ, Boura J, et al. Does beta-bloquer therapy improbé clinical outcomes of acute myocardial infarction after successful primary angioplasty? A pooled análisis from the primary angioplasti in myocardial infarction-2 (PAMI-2), No surgery on-site

(noSOS), stetn PAMI and Air PAMI trials. Circulation. 2003;108(Suppl IV):416–7.
22. Scheuble A, Emery M, López-Sendón J, de Lopez Sa E, Fondard O, Dabbous OH, Eagle KA, Anderson FA, Steg PG. Patterns of early use of intravenous and oral beta-blockers in ST-segment elevation myocardial infarction in the reperfusion era. The Global Registry of Acute Coronary Events. Eur Heart J. 2005;26(Abstract Suppl):159.
23. Gottlieb S, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. Circulation. 1986;3:331–7.
24. Telford A, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. Lancet. 1981;1:1225–8.
25. Lubsen JTJ. Effcacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). Am J Cardiol. 1987;60:18A–25.
26. Yusuf S, Witte J, Friedman L. Overview of results of randomized trials in heart disease: unstable angina, heart failure, primary prevention with aspirin and risk factor modifications. JAMA. 1988;260:2259–63.
27. Gottlieb S, McCarter R, Vogel R. Effect of beta-blockade on mortality among high risk patients after myocardial infarction. N Engl J Med. 1998;338:489–97.
28. Ellis K, Tcheng JE, Sapp S, Topol EJ, Lincoff AM. Mortality benefit of beta blockade in patients with acute coronary syndromes undergoing coronary intervention: pooled results from the Epic, Epilog, Epistent, Capture and Rapport Trials. J Interv Cardiol. 2003;16:299–305.
29. Emery M, López-Sendón J, Steg PG, Anderson Jr FA, Dabbous OH, Scheuble A, Eagle KA. Patterns of use and potential impact of early beta-blocker therapy in non-ST-elevation myocardial infarction with and without heart failure: the Global Registry of Acute Coronary Events. Am Heart J. 2006;152:1015–21.
30. Tilmant PY, Lablanche JM, Thieuleux FA, et al. Detrimental effect of propranolol in patients with coronary arterial spasm countered by combination with diltiazem. Am J Cardiol. 1983;52:230–3.
31. Members of the CAPRICORN Steering Committee on behalf of the investigators and committees. CAPRICORN. Effect of carvedilol on outcome after myocardial infarction in patients with left ventricular dysfunction. Lancet. 2001;357:1385–90.
32. Church J, Zsotér T. Calcium antagonistic drugs. Mechanism of action. Can J Physiol Pharmacol. 1980;58:254–64.
33. The Danish Study Group on Verapamil in Myocardial Infarction. Verapamil in acute myocardial infarction. Eur Heart J. 1984:5;516–28.

34. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghiad M, Capone RJ, Crawford MH, Schlant RC, Kleiger RE. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. N Engl J Med. 1986;315:423.
35. Boden W, Gilst W, Scheldewaert R, Starkey S, Carlier M, Julian D, Whitehead A, Bertrand M, Col J, Pedersen O, Lie K, Santoni JP, Fox KM and for the Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis post-Thrombolysis (INTERCEPT). Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo controlled trial. Lancet. 2000;355:1751–6.
36. Muller JE, Morrison J, Stone PH, Rude RE, Rosner B, Roberts R, Pearle DL, Turi ZG, Schneider AD, Serfas DH. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. Circulation. 1984;69:740–7.
37. Torfgård KE, Ahlner J. Mechanisms of action of nitrates. Cardiovasc Drugs Ther. 1994;8:701–17.
38. Klemenska E, Beresewicz A. Bioactivation of organic nitrates and the mechanism of nitrate tolerance. Cardiol J. 2009;16:11–9.
39. Jugdutt BI, Warnica JW. Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion, and complications. Effect of timing, dosage, and infarct location. Circulation. 1988;78:906–19.
40. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet. 1994;343: 1115–22.
41. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet. 1995;345:669.
42. The ESPRIM trial: short-term treatment of acute myocardial infarction with molsidomine. European Study of Prevention of Infarct with Molsidomine (ESPRIM) Group. Lancet. 1994;344:91–7.
43. Ren Z, Yang Q, Floten HS, Furnary AP, Yim AP, He GW. ATP-sensitive potassium channel openers may mimic the effects of hypoxic preconditioning on the coronary artery. Ann Thorac Surg. 2001;71:642–7.
44. Kitakaze M, Asakura M, Kim J, Shintani Y, Asanuma H, Hamasaki T, et al. for the J-WIND Investigators. Human atrial natriuretic peptide and nicorandil as adjuncts to reperfusion treatment for acute myocardial infarction (J-WIND): two randomised trials. Lancet. 2007;370:1483–93.

45. Iwakura K, Ito H, Okamura A, Yasushi Koyama Y, Date M, Higuchi Y, et al. Nicorandil treatment in patients with acute myocardial infarction. A meta-analysis. Circ J. 2009;73:925–31.
46. Zaza A, Belardinelli L, Shryock JC. Pathophysiology and pharmacology of the cardiac late sodium current. Pharmacol Ther. 2008;119:326–39.
47. Morrow D, Scirica B, Karwatowska E, Murphy E, Budja A, Varshavsky S, et al. Effects of ranolazine on recurrent cardiovascular events in patients with non–ST-elevation acute coronary syndromes he MERLIN-TIMI 36 randomized trial. JAMA. 2007;297:1775–83.
48. Wilson S, Scirica B, Braunwald E, Murphy S, Karwatowska E, Buros L, Chaitman B, Morrow D. Observations from the randomized, double-blind, placebo-controlled MERLIN–TIMI(metabolic efficiency with ranolazine for less ischemia in non–ST-segment elevation acute coronary syndromes) 36 trial. J Am Coll Cardiol. 2009;53:1510–6.
49. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme a thiolase. Circ Res. 2000;86:580–8.
50. The EMIP-FR Group. European Myocardial Infarction Project--Free Radicals. Effect of 48-h intravenous trimetazidine on short- and long-term outcomes of patients with acute myocardial infarction, with and without thrombolytic therapy; A double-blind, placebo-controlled, randomized trial. Eur Heart J. 2000;18:1537–46.
51. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez-Sendon J, Steg PG, Tardif JC, Tavazzi L, Tendera M. Resting heart rate in cardiovascular disease. J Am Coll Cardiol. 2007;50:823–30.
52. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van de Werf F, Avezum Á, Goodman SG, Flather MD, Fox KAA, for the Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med. 2003;163:2345–53.
53. Yan AT, Yan RT, Tan M, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J. 2007;28:1072–8.
54. Herman M, Donovan J, Tran M, et al. Use of beta-blockers and effects on heart rate and blood pressure post-acute coronary syndromes: are we on target? Am Heart J. 2009;158:378–85.
55. Hjalmarson A, Gilpin EA, Kjekshus J, Chieman G, Nicod P, Henning H, et al. Influence of heart rate on mortality after acute myocardial infarction. Am J Cardiol. 1990;65:547–53.