Current Cardiovascular Therapy
Series Editor: Juan Carlos Kaski

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Peter Clemmensen *Editors*

Pharmacological Treatment of Acute Coronary Syndromes

ISCP
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ISCP
International Society of Cardiovascular Pharmacotherapy

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This book is dedicated to Prof. Juan Carlos Kaski, President of ISCP

Series Preface

Cardiovascular pharmacotherapy is of fundamental importance for the successful management of patients with cardiovascular diseases. Appropriate therapeutic decisions require a proper understanding of the disease and a thorough knowledge of the pharmacological agents available for clinical use. The issue is complicated by the existence of large numbers of agents with subtle differences in their mode of action and efficacy and the existence of national and international guidelines, which sometimes fail to deliver a clear-cut message. Aggressive marketing techniques from pharma industry; financial issues at local, regional, or national levels; and time constraints make it difficult for the practitioner to – at times – be absolutely certain as to whether drug selection is absolutely appropriate. The International Society of Cardiovascular Pharmacotherapy (ISCP) aims at supporting evidence-based, rational pharmacotherapy worldwide. This book series represents one of its vital educational tools. The books in this series aim at contributing independent, balanced, and sound information to help the busy practitioner to identify the appropriate pharmacological tools and to deliver rational therapies. Topics in the series include all major cardiovascular scenarios, and the books are edited and authored by experts in their fields. The books are intended for a wide range of healthcare professionals and particularly for younger consultants and physicians in training. All aspects of pharmacotherapy are tackled in the series in a concise and practical fashion. The books in this series provide a unique set of guidelines and examples that will prove valuable for patient management. They clearly articulate many of the dilemmas

clinicians face when working to deliver sound therapies to their patients. The series will most certainly be a useful reference for those seeking to deliver evidence-based, practical, and successful cardiovascular pharmacotherapy.

Juan Carlos Kaski, DSc, DM (Hons),
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ISCP Current Cardiovascular Therapy Series

Preface

Acute coronary syndromes (ACS) require rapid intervention with pharmacologic therapies to treat and prevent coronary thromboembolism, and is essential to prepare the patient for revascularization procedures, especially percutaneous coronary intervention. The aims of treatment are to preserve patency of the coronary artery, augment blood flow through stenotic lesions, and reduce myocardial oxygen demand. Conventional treatment includes anti-ischemic, antiplatelet and anticoagulant therapy. All patients should receive antiplatelet agents, and patients with evidence of ongoing ischemia should receive aggressive medical intervention until signs of ischemia, as determined by symptoms and ECG, resolve. After a decade of relatively few advances in antithrombotic treatment, the clinical availability of potent new inhibitors of $P2Y_{12}$ platelet receptors has changed the ACS treatment paradigm. The most recent AMI – STEMI and NSTE-ACS guidelines of the European Society of Cardiology (ESC) have recommended ticagrelor and prasugrel in preference to clopidogrel for ACS patients, but globally clopidogrel is expected to remain a dominant therapy for the years to come. Furthermore, a group of novel oral anticoagulant and antiplatelet agents are promising for the acute management and secondary prevention in ACS. Triple therapy, while not initiated in the acute setting, may impact on future surgical and medical emergencies, and their management including bleeding complication should be known to health professionals across a wide spectrum of specialties. The ESC guidelines recommendations also differ for each of the antiplatelet and anticoagulant agent in terms of patient selection, pretreatment

and timing of therapy; reflecting differences in the patient populations that were studied and the dissimilar safety profiles that emerged from trials. An unavoidable untoward consequence of increased antithrombotic effectiveness has been an increased risk, mostly in terms of bleeding.

The goal of this book is to update clinicians on the most recent data regarding the medical management of ACS patients. The authors have provided useful information and expert opinion that take into account results of large trials, European and American Guidelines, and real-life, day-to-day clinical practice.

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Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
APPRAISE-2	The Apixaban for Prevention of Acute Ischemic Events 2
ATLAS ACS 2-TIMI 51	The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51
ATRIA	Anticoagulation and Risk Factors in Atrial Fibrillation
BARC	Bleeding Academy Research Consort
CHA_2DS_2VASc	Congestive heart failure or left ventricular dysfunction hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, Sex category (female)
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of ACC/AHA Guidelines
CURE	The Clopidogrel in Unstable Angina to Prevent Recurrent Events
GRACE	The Global Registry of Acute Coronary Events

HAS-BLED	Hypertension Abnormal Renal/ Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol
HEMORR(2)HAGES	Hepatic or Renal Disease Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke
IHD	Ischemic heart disease
INR	International Normalized Ratio
MI	Myocardial infarction
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
PLATO	The Study of Platelet inhibition and Patient Outcomes
PPI	Proton-pump inhibitors
RELY	The Randomized Evaluation of Long-Term Anticoagulation Therapy
STEMI	ST elevation myocardial infarction
TRITON-TIMI 38	Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
UA	Unstable angina
WOEST	The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

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.

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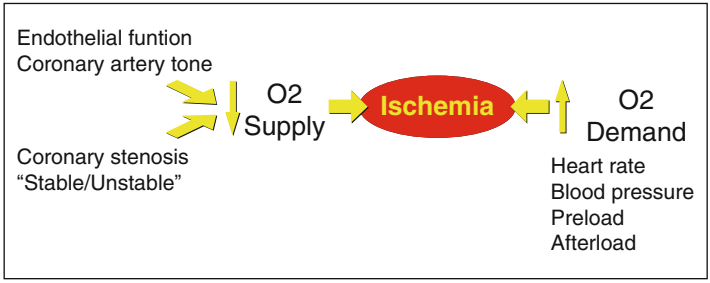


FIGURE 1.1 Myocardial ischemia is the result of multiple possible etiologies that may contribute to an imbalance in myocardial oxygen supply and demand

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

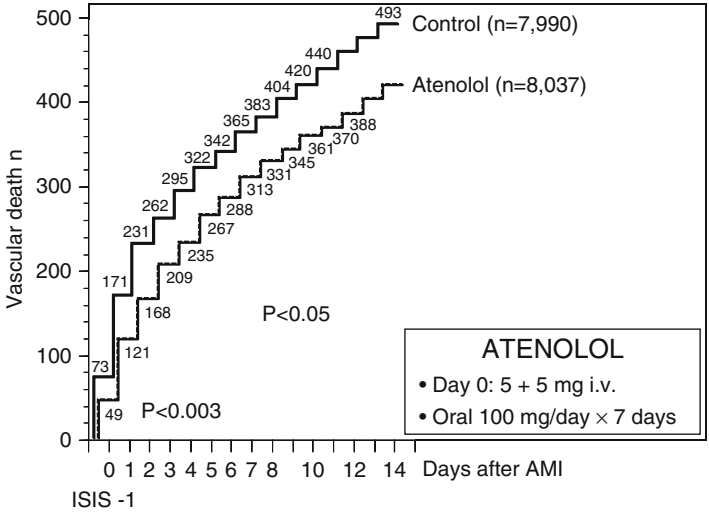


FIGURE 1.2 Cumulative vascular mortality in the groups of patients allocated to atenolol and placebo in the ISIS-1 trial (Reprinted with permission from ISIS-1 (First International Study of Infarct Survival) Collaborative Group [8])

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

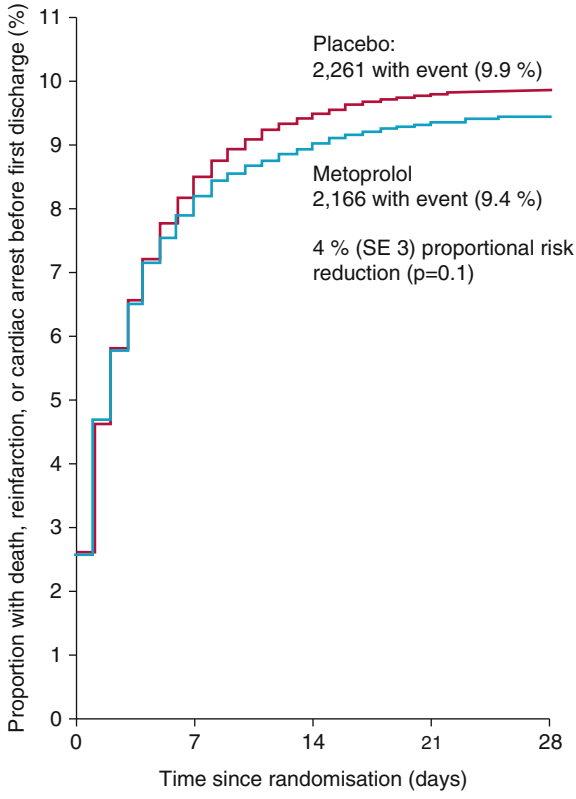
Three trials of randomised iv beta-blockade were conducted after the widespread use of reperfusion therapy in AMI [13–15], but the number of events was too small to establish clear conclusions. In the second Thrombolysis in Myocardial Infarction (TIMI-II) trial [13], thrombolysed patients were randomly 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].

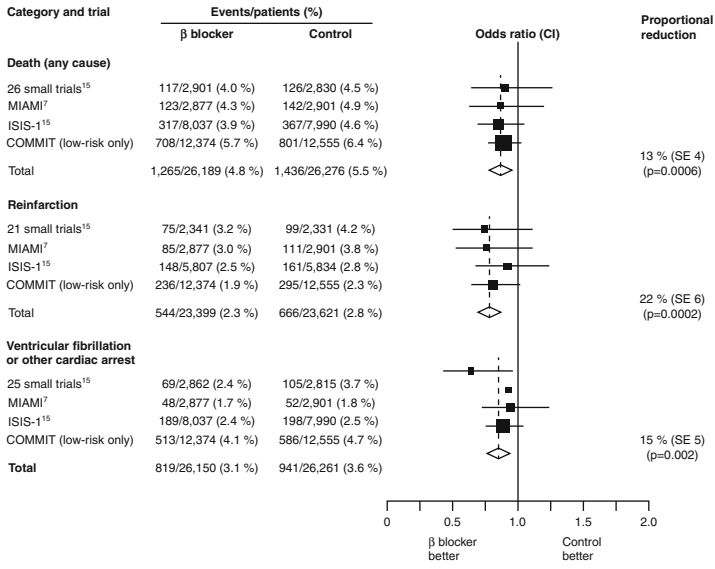


FIGURE 1.4 Metaanalysis of betablockers in patients with acute myocardial infarction, demonstrating a benefit in outcomes: mortality, myocardial infarction and ventricular fibrillation or other cardiac arrest (Reprinted with permission from COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction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