Cardiac Drug Therapy

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Cardiac Drug Therapy

Seventh Edition

by

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Dedication

To My wife Brigid
and
To our children
Susan, Christine, Yasmin, Stephen, Jacqueline, and Natasha

PREFACE

The impetus to provide a seventh edition of *Cardiac Drug Therapy* was generated by the positive comments received from readers worldwide, and from favorable reviews of earlier editions. The seventh edition updates and revises the sixth edition in several respects. In particular, the text includes: Six new chapters that deal with ongoing important controversies regarding the use of several widely used cardiac drugs.

Controversies have arisen regarding the use of beta blockers for the treatment of hypertension. The front cover of *The Lancet* November 4, 2005 highlighted "beta blockers should not remain first choice in the treatment of primary hypertension." Is this statement true or false? In addition Trialists have indicated that beta blockers and diurectics cause an increased incidence of new diabetes; it appears that most experts in the field have endorsed this information. In the *Lancet*, January 2007, another faulty metaanalysis provides the same misleading information.

- The chapter Beta-Blocker Controversies gives substantial evidence that indicates to Clinicians that both preceding statements are false. In the chapter Beta-blockers, a section is given entitled "Which Beta Blocker is Best for Your Patients?"

New chapters include:

- ACE Inhibitor Controversies.
- Calcium Antagonist Controversies: The controversies regarding the use of calcium antagonists are further analyzed and clear directions are given to clinicians regarding when to choose a calcium antagonist, and which one to choose.
- Hypertension Controversies. There are more than one billion hypertensive individuals requiring drug therapy and only four classes of antihypertensive agents are available: diuretics, beta blockers, ACE inhibitors/angiotensin receptor blockers, and calcium antagonists. Alpha blockers and centrally acting agents have limited use. If it is true that both beta blockers and diuretics cause an increased incidence of new onset diabetes, then patient treatment would be compromised. Physicians worldwide are perplexed. This important area is clarified and treatment algorithms are given for the choice of drug based on the age and ethnicity of the hypertensive patient.
- The chapter Heart Failure Controversies discusses : heart failure preserved ejection fraction; is the combination of ACE inhibitor or ARB genuinely beneficial ? Recommended heart failure agents all cause bothersome lowering of blood pressure. Digoxin has been discarded by most who fail to recall that this is the only heart failure drug that does not lower blood pressure, and it can be used without causing toxicity because salutary effects are obtained with low serum digoxin levels 0.5–0.9 ng/mL particularly in patients with class III-IV heart failure.
- The chapter Statin Controversies explores rhabdomyolysis , interactions, and other issues.
- The chapter Hallmark Clinical Trials has been expanded to accommodate the wealth of practical information derived from these studies.

As in all previous editions, therapeutic strategies and advice are based on a thorough review of the scientific literature, applied logically:

- Scientific documentation regarding which drugs are superior.
- Information on which cardiovascular drugs to choose and which agents to avoid in various clinical situations.
- Information that assists with the rapid writing of prescriptions. To write a prescription accurately, a practitioner needs to know how a drug is supplied and its dosage. Thus, supply and dosage are given first, followed by action and pharmacokinetics, then advice as to efficacy and comparison with other drugs, indications, adverse effects, and interactions.
- The name of each drug, the formulation, and the dosage have been put in tabular format; this allows quick retrieval of the information required when writing prescriptions.
- An appendix provides a global table of cardioactive drugs with their generic and tradenames in North America, the UK, Europe, and Japan.
- The text contains practical advice, such as the following:

  The life-saving potential of 75–160 mg chewable aspirin is denied to many individuals who succumb to an acute coronary syndrome because of poor dissemination of clinically proven, documented facts. The text advises: two ~ 80 mg chewable aspirins should be placed in the cap of a nitrolingual spray container to be used before proceeding to an emergency room. Clinicians should inform patients that rapidly acting chewable aspirin may prevent a heart attack or death but that nitroglycerin does not.

  The dosages of drugs given in the text apply to the adult and are standard. Often, a lower dose than the manufacturer's recommended maximum is advised because in clinical practice a lesser dose suffices and results in fewer adverse effects, especially when medications are combined.

The information provided in the seventh edition should serve as a refresher for cardiologists and internists. The information should improve the prescribing skills of medical residents, general practitioners, and all who care for patients with cardiac problems.

Acknowedgments: First to Paul Dolgert Publishing Director at Humana Press, whom I sought to publish this work because he is without equal at his craft. He has made my book *Heart Disease Diagnosis and Therapy* a success and has agreed to do more for *Rapid ECG Interpretation* to be published in 2008. I thank him particularly for agreeing to display my material in a more user friendly format than that of the sixth edition. The pages are wider and the font enlarged. Now, crucial information can be rapidly retrieved and I feel fulfilled.

Also, to James Geronimo who expertly guided me through the production concerns and to Lisa Bargeman. *Lastly, a special, thank you, to my wife Brigid, who has allowed me to be a student of the science of Medicine to this day.*

M. Gabriel Khan, *MD*

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About the Author

Dr. M. Gabriel Khan is a cardiologist at the Ottawa Hospital and an Associate Professor of Medicine, at the University of Ottawa. Dr. Khan graduated MB, BCh, with First-Class Honours at The Queen's University of Belfast. He was appointed Staff Physician in charge of a Clinical Teaching Unit at the Ottawa General hospital and is a Fellow of the American College of Cardiology, the American College of Physicians, and the Royal College of Physicians of London and Canada. He is the author of *On Call Cardiology*, 3rd ed., Elsevier, Philadelphia (2006); *Heart Disease Diagnosis and Therapy,* 2nd ed., Humana Press (2006); *Rapid ECG Interpretation*, 2nd ed., Elsevier, Philadelphia, PA (2003); and *Cardiac and Pulmonary Management* (1993), *Medical Diagnosis and Therapy* (1994), *Heart Attacks, Hypertension and Heart Drugs* (1986), *Heart Trouble Encyclopedia* (1996), and *Encyclopedia of Heart Diseases* (2006), Academic Press/ Elsevier, San Diego.

Dr. Khan's books have been translated into Chinese, Czech, Farsi, French, German, Greek, Italian, Japanese, Polish, Portuguese, Russian, Spanish, and Turkish. He has built a reputation as a clinician-teacher and has become an internationally acclaimed cardiologist through his writings.

His peers have acknowledged the merits of his books by their reviews of *Cardiac Drug Therapy*: Review of the 5th edition in *Clinical Cardiology*: "this is an excellent book. It succeeds in being practical while presenting the major evidence in relation to its recommendations. Of value to absolutely anyone who prescribes for cardiac patients on the day-to-day basis. From the trainee to the experienced consultant, all will find it useful. The author stamps his authority very clearly throughout the text by very clear assertions of his own recommendations even when these recommendations are at odds with those of official bodies. In such situations the 'official' recommendations are also stated but clearly are not preferred."

And for the fourth edition a cardiologist reviewer states that it is "by far the best handbook on cardiovascular therapeutics I have ever had the pleasure of reading. The information given in each chapter is up-to-date, accurate, clearly written, eminently readable and well referenced."

1 Beta-Blockers

The Cornerstone of Cardiac Drug Therapy

NEW CONCEPTS

This chapter tells you

- Which beta-blocker is best for your patients.
- The pharmacodynamic reasons why atenolol is a relatively ineffective beta-blocker and why the use of atenolol should be curtailed.
- More about the important indication for heart failure (HF), New York Heart Association (NYHA) class II–III and now compensated class IV, and for all with left ventricular (LV) dysfunction regardless of functional class; thus, in class I patients with an ejection fraction (EF) < 40% and in those with myocardial infarction (MI) with HF or LV dysfunction without HF, beta-blockers are recommended at the same level as angiotensin-converting enzyme (ACE) inhibitors.
- *Why beta-blockers should be recommended for diabetic patients with hypertension with or without proteinuria* and for diabetic patients with coronary heart disease (CHD). From about 1990 to 2002, most internists proclaimed in editorials and to trainees that these agents were a poor choice in this setting.
- More recently, their use as initial agents for the treatment of primary hypertension has been criticized, particularly for diabetics with hypertension; do beta-blocking drugs cause diabetes or is the condition observed, simply, benign glucose intolerance in some? (*See* Chapter 2, Beta-Blocker Controversies.)
- Why is it incorrect to say that *beta-blockers are not advisable for hypertensive patients over age 65*, as many teachers, textbooks, and editorials state. This was reiterated in an editorial by Cruickshank entitled "Beta-blockers continue to surprise us" *(1)*.
- The results of randomized clinical trials (RCTs) that prove the lifesaving properties of these agents.
- All their indications.
- Salient points that relate to each beta-blocker and show the subtle and important differences confirming that beta-blockers are not all alike. Beta-blockade holds the key, but lipophilic versus hydrophilic features may be important, and brain concentration may enhance cardioprotection.

Four classes of oral agents have been shown in RCTs to decrease cardiovascular morbidity and mortality:

- Beta-blockers.
- Aspirin and clopidogrel.
- ACE inhibitors or angiotensin II receptor blockers (ARBs).
- Statins.

From: *Contemporary Cardiology: Cardiac Drug Therapy, Seventh Edition*
M. Gabriel Khan © Humana Press Inc., Totowa, NJ

Beta-blockers are now recommended and used by virtually all cardiologists because they are necessary for the management of acute and chronic ischemic syndromes, manifestations of CHD. The statins have been added to the list of proven agents.

The approximate lifesaving potentials of these agents are as follows:

- Beta-blockers: approx 33%; **they enhance the salutary effects of ACE inhibitors**; in mild to moderate HF, average mortality reduction for beta-blockers is 36% versus 21% for ACE inhibitors.
- Aspirin: 23%.
- ACE inhibitors: 20%.
- Statins: approx 15%.

Many internists and family physicians, however, remain reluctant to prescribe beta-blockers in many cardiovascular situations including HF, in hypertension in patients aged >65 years, and in diabetic patients. Other agents, particularly calcium antagonists, are used in preference mainly because of fears engendered by the pharmaceutical firms that market calcium antagonists and ACE inhibitors.

- It is noteworthy that a body as illustrious as the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) advised against the use of beta-blockers in hypertensive patients with diabetes or dyslipidemia *(2)*. It appears that these views are similar to those of most internists and family physicians.
- For many years (1989–2002), the JNC advised physicians to use alpha-blockers for the treatment of hypertension in patients with dyslipidemia because these agents do not alter lipid levels unfavorably *(2)*. The JNC only advised in 2002 against the use of alpha-blockers after it was shown that the alpha-blocker doxazosin caused a marked increase in the incidence of HF in treated hypertensive patients. In 1988, the second edition of the present text issued a warning regarding the use of alpha-blockers.

In the setting of dyslipidemia, editorials, textbooks, internists, and committee guidelines of the World Health Organization (WHO) and the JNC have recommended agents other than beta-blockers, but beta-blockers are *not* contraindicated in dyslipidemia.

Fears that beta-blockers influence lipid levels unfavorably are unfounded. Beta-blocking drugs do not alter low-density lipoprotein (LDL) levels; they may cause a mild increase in levels of triglycerides and may produce a 1% to approx 6% lowering of high-density lipoprotein cholesterol (HDL-C) in fewer than 10% of patients treated *(3)*. The alteration in HDL-C levels is of minimal clinical concern because the effect is so small, if it occurs at all *(4)*. The clinical importance of this mild disturbance in lipid levels is of questionable significance and should not submerge the prolongation of life and other salutary effects obtained with the administration of beta-blocking drugs (Fig. 1-1).

Since their original discovery by Sir James Black at Imperial Chemical Industries in the United Kingdom *(5)* and the introduction of the prototype, propranolol, for the treatment of hypertension in 1964 by Prichard and Gillam *(6)*, more than 12 beta-blocking drugs have become available.

The first edition of *Cardiac Drug Therapy* in 1984 included a table entitled "Beta-blockers: first-line oral drug treatment in angina pectoris" (Table 1-1); this table indicated the superiority of beta-blockers over calcium antagonists and nitrates. Calcium antagonists were downrated because they decreased blood flow to subendocardial areas; in addition, in the condition for which they were developed, coronary artery spasm (CAS), they were not shown to decrease mortality. This table has never been altered. The 1990s have shown the possible adverse effects and potential dangers of dihydropyridine

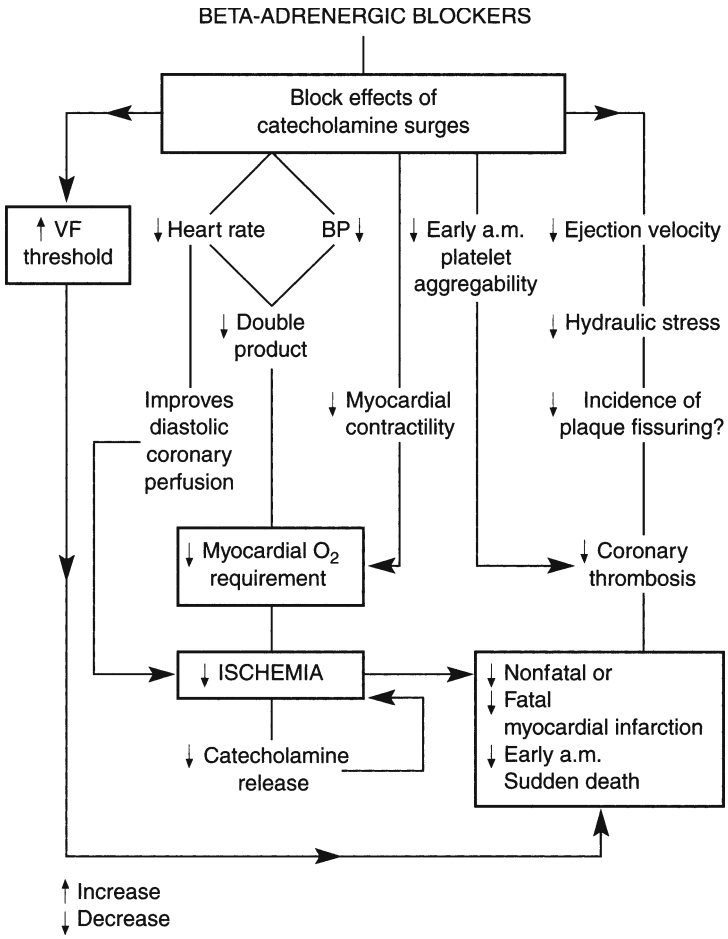

Fig. 1-1. Salutary effects of beta-adrenergic blockade. (From Khan M Gabriel, Topol EJ. Acute myocardial infarction diagnosis and therapy, a practical approach. Philadelphia, PA, Williams and Wilkins, 1996.)

Table 1-1
Beta-Blockers: First-Line Oral Drug Treatment in Angina Pectoris

Effect on	*Beta-blocker*	*Calcium antagonist*	*Oral nitrate*
Heart rate	↓	↑↓	↓
Diastolic filling of coronary arteries	↑	—	—
Blood pressure	↓↓	↓↓	—
Rate pressure product (RPP)	↓	—[a]	—
Relief of angina	Yes	Yes	Variable
Blood flow (subendocardial ischemic area)[b]	↑	↓	Variable
First-line treatment for angina pectoris	Yes	No	No
Prevention of recurrent ventricular fibrillation	Proven	No	No
Prevention of cardiac death	Proven	No	No
Prevention of pain owing to CAS	No	Yes	Variable
Prevention of death in patient with CAS	No	No	No

[a]RPP variable decrease on exercise, but not significant at rest or on maximal exercise.
[b]Distal to organic obstruction *(40)*.
CAS, coronary artery spasm; ↓, decrease; ↑, increase; —, no significant change.

Table 1-2
Beta-Blockers: Randomized Controlled Trials Showing Significant Reduction in Mortality Rate

		Mortality		*Relative risk reduction*	
Trial	*Drug*	*Placebo*	*Drug*	*%*	*P*
APSI *(39)*	Acebutolol	34/309 11.0%	17/298 5.7%	48	0.019
BHAT *(31)*	Propranolol	188/1921 9.8%	138/1916 7.2%	26.5	<0.01
Norwegian Postinfarction Study *(16)*	Timolol	152/939 16.2%	98/945 10.4%	35.8	<0.001
Salathia	Metoprolol	43/364 11.8%	27/391 6.9%	41.5	<0.05
Hjalmarson et al. *(69)*	Metoprolol Post Ml	62/679 8.9%	40/698 5.7%	36.0	<0.03
COPERNICUS					
CAPRICORN					
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MERIT-HF					

calcium antagonists. Dihydropyridines increase the risk of death in patients with unstable angina; these agents are not approved for use in unstable angina in the absence of beta-blockade. Diltiazem and verapamil have been shown to increase mortality in patients with acute MI with LV dysfunction *(7)*. After more than 25 yr of use, calcium antagonists have not been shown in RCTs to prolong life significantly in patients with CHD. Beta-blockers have been shown to prolong life in more than four RCTs (Table 1-2). Because calcium antagonists have been shown to increase cardiovascular mortality in hypertensive diabetic patients *(8)*, the author strongly recommends the use of beta-blockers except in diabetic patients prone to hypoglycemia. This recommendation is in accordance with those of most cardiologists and differs from that of the JNC. Diabetic patients can be given a cardioselective beta-blocker *(4)* or an ACE inhibitor.

This chapter provides information that includes

- Sound reasons and results of RCTs that document the salutary effects of beta-blockers in many cardiovascular settings (Tables 1-1, 1-2, and 1-3).
- The appropriate indications as advocated by virtually all cardiologists.

The many approved cardiovascular indications (Table 1-3) allow the author to proclaim that beta-blockers are the cornerstone of cardiac drug therapy. As a class, beta-blockers represent one of the five all-time major breakthroughs in clinical drug development *(4)*. Virtually all cardiologists now concur with the author's views on the salutary effects of beta-blockers.

BETA-RECEPTORS

The beta-receptors are subdivided into

- The $beta_1$-receptors, present mainly in the heart, intestine, renin-secreting tissues of the kidney, those parts of the eye responsible for the production of aqueous humor, adipose tissue, and, to a limited degree, bronchial tissue.

Table 1-3
Cardiovascular Indications for Beta-Blockers

1. Ischemic heart disease
   Stable angina
   Unstable angina
   Acute Ml
   Ml, long-term prevention
   Silent ischemia
2. Arrhythmias
   VPBs
   AVNRT
   Atrial fibrillation
   Nonsustained VT
   VT
   Recurrent VF
3. Hypertension
   Isolated
   With IHD, diabetes*, LVH, dyslipidemia[a]
   With arrhythmias
   Perioperative and on intubation
   Severe, urgent
   Pheochromocytoma (on alpha-blocker)
4. Heart failure: new indication class I–III
5. Prolonged QT syndrome
6. Aortic dissection
7. Valvular heart disease
   Mitral stenosis? tachycardia in pregnancy*
   Mitral valve prolapse
   Mitral regurgitation
8. To decrease perioperative mortality
9. Cardiomyopathy
   Hypertrophic
   Dilated
10. Marfan's syndrome
11. Neurocardiogenic syncope
12. Tetralogy of Fallot
13. Aneurysm

[a]*See* text; 10-yr CHD event risk score > 20%; *see* Chapter 17.

AVNRT, atrioventricular node reentry tachycardia; CHD, coronary heart disease; IHD, ischemic heart disease; LVH, left ventricular hypertrophy; VPB, ventricular premature beat; VF, ventricular fibrillation; VT, ventricular tachycardia.

- The beta$_2$-receptors, predominating in bronchial and vascular smooth muscle, gastrointestinal tract, the uterus, insulin-secreting tissue of the pancreas, and, to a limited degree, the heart and large coronary arteries. Metabolic receptors are usually beta$_2$. In addition, it should be noted that
  a. None of these tissues contains exclusively one subgroup of receptors.
  b. The beta-receptor population is not static, and beta-blockers appear to increase the number of receptors during long-term therapy. The number of cardiac beta$_2$-receptors increases after beta$_1$-blockade *(9)*.
  c. The population density of receptors decreases with age.

The beta-receptors are situated on the cell membrane and are believed to be a part of the adenyl cyclase system. An agonist acting on its receptor site activates adenyl cyclase to produce cyclic adenosine-5'-monophosphate, which is believed to be the intracellular messenger of beta-stimulation.

The heart contains $beta_1$- and $beta_2$-adrenergic receptors in the proportion 70:30. Normally, cardiac $beta_1$-adrenergic receptors appear to regulate heart rate and/or myocardial contractility, but in situations of stress, with the provocation of epinephrine release, stimulation of cardiac $beta_2$-receptors may contribute to additional increases in heart rate and/or contractility *(10)*. In HF, cardiac $beta_1$- but not $beta_2$-adrenergic receptors are reduced in number and population, and the myocardium may be less responsive to $beta_1$-inotropic agents.

MECHANISM OF ACTION

By definition, beta-blockers block beta-receptors. Structurally, they resemble the catecholamines. Beta-blockers are competitive inhibitors, their action depending on the ratio of beta-blocker concentration to catecholamine concentration at beta-adrenoceptor sites.

- Blockade of cardiac $beta_1$-receptors causes a decrease in heart rate, myocardial contractility, and velocity of cardiac contraction. The heart rate multiplied by the systolic blood pressure (i.e., the rate pressure product [RPP]) is reduced at rest and during exercise, and this action is reflected in a reduced myocardial oxygen demand (which is an important effect in the control of angina).
- The main in vitro antiarrhythmic effect of beta-blockers is the depression of phase 4 diastolic depolarization. Beta-blockers are effective in abolishing arrhythmias produced by increased catecholamines. Maximum impulse traffic through the atrioventricular (AV) node is reduced, and the rate of conduction is slowed. Paroxysmal supraventricular tachycardia (PSVT) caused by AV nodal reentry is often abolished by beta-blockers, which also slow the ventricular rate in atrial flutter and atrial fibrillation. There is a variable effect on ventricular arrhythmias, which may be abolished if induced by increased sympathetic activity, as is often seen in myocardial ischemia.
- Beta-blockers reduce the activity of the renin-angiotensin system by reducing renin release from the juxtaglomerular cells. Also, beta-blockade augments atrial and brain natriuretic peptide (see next section and Suggested Reading).
- Beta-blockers interfere with sympathetic vasoconstrictor nerve activity; this action is partly responsible for their antihypertensive effect. Cardiac output usually falls and remains slightly lower than normal with administration of nonintrinsic sympathomimetic activity (ISA) agents. Systemic vascular resistance increases acutely but falls to near normal with long-term administration *(14)*.

Other Important Clinically Beneficial Mechanisms

Beta-blockers

- Lower plasma endothelin-1 levels, as shown for carvedilol *(11)*, and inhibit catecholamine-induced cardiac necrosis (apoptosis) *(12)*.
- Stimulate the endothelial-*arginine/nitric oxide pathway*, as shown for the interesting vasodilatory beta-blocker nebivolol *(13)*. (*See* last section "Which Beta-Blocker Is Best for Your Patients?".)
- Augment atrial and brain natriuretic peptide, upregulate cardiac $beta_1$-receptors, and inhibit stimulatory anti-$beta_1$-receptor autoantibodies.

Beta-Blocker Effect on Calcium Availability

The slow channels represent two of the mechanisms by which calcium gains entry into the myocardial cell. At least two channels exist *(15)*, namely,

- A voltage-dependent channel blocked by calcium antagonists (*see* Chapter 8).
- A receptor-operated channel blocked by beta-receptor blockers that therefore decrease calcium availability inside the myocardial cell. The negative inotropic effect of beta- blockers is probably based on this effect.

DOSAGE CONSIDERATIONS

- The **beta-blocking effect** is manifest as a blockade of tachycardia when induced by exercise or isoproterenol. The therapeutic response to beta-blockers does not correlate in a linear fashion with the oral dose or plasma level. Differences in the degree of absorption and variation in hepatic metabolism give rise to unpredictable plasma levels, but in addition the same blood level may elicit a different cardiovascular response in patients, depending on the individual's sympathetic and vagal tone and the population of beta-receptors.
- The **dose** of beta-blocker is titrated to achieve control of angina, hypertension, or arrhythmia. The dose is usually adjusted to achieve a heart rate of 50–60/min and an exercise heart rate < 110/min. The dosage of propranolol varies considerably (120–480 mg daily) because of the marked but variable first-pass hepatic metabolism. There is a 20-fold variation in plasma level from a given dose of this drug. The proven **cardioprotective** (CP) dose may be different from the dose necessary to achieve control of angina or hypertension. The effective CP dose (i.e., the dose shown to prevent cardiac deaths in the post-MI patient) for timolol is 10–20 mg daily *(16)*, and for propranolol it is within the range 160–240 mg daily. When possible, the dosage of beta-blocker should be kept within the CP range. Other experts are in agreement with this concern for use of the CP dose when possible *(17)*.
- An **increase in the dose** beyond the CP dosage (e.g., timolol > 30 mg or propranolol > 240 mg daily), for better control of angina, hypertension, or arrhythmia, may have a poor reward, that is, there could be an increase in side effects, especially dyspnea, HF, and distressing fatigue.
- A review of the clinical literature reveals that too large a dose of beta-blockers may be not only nonprotective but also positively harmful, and this is supported by studies on animals *(18)*. In some patients, one should be satisfied with 75% control of symptoms and, if necessary, the addition of a further therapeutic agent. The patient is not fearful of anginal pain or high blood pressure—what the patient fears is death. *Beta-blockers do prevent cardiac deaths, but they have been shown to do so only at certain doses*. In addition, beta-blockers are not all alike; subtle differences can be of importance. Only bisoprolol, carvedilol, metoprolol, propranolol, and timolol have been shown to prolong life in RCTs (*see* Table 1-2).
- Patients may require different drug concentrations to achieve adequate beta-blockade because of different levels of sympathetic tone (circulating catecholamines and active beta-adrenoceptor binding sites). However, **plasma levels** do not indicate active metabolites, and the effect of the drug may last longer than is suggested by the half-life.
- Propranolol may take 4–6 wk to achieve stable plasma levels because of the extensive hepatic metabolism, but timolol and pindolol undergo less than 60% metabolism, and constant plasma concentrations are more readily achieved. Therefore, **propranolol** should be given three times daily for about 6 wk and then twice daily, or propranolol long-acting (LA) 160–240 mg once daily.
- **Atenolol**, **nadolol**, and **sotalol** are excreted virtually unchanged by the kidneys and require alteration of the dosage in severe renal dysfunction, as follows:

Table 1-4
Dosage of Commonly Used Beta-Blockers

Beta-blocker	*Daily starting dose (mg)*	*Maintenance dose (mg)*	*Maximum suggested dose (mg)*
Atenolol*	50	50–100	100
Acebutolol	100–400	600–1000	1200
Bisoprolol	5	5–15	20
Carvedilol	12.5	25–50	50
Metoprolol	50–100	100–300	400
Nadolol	20–80	20–160	160
Propranolol	40–120	40–240	320
Sotalol	80–160	60–320	320
Timolol	5–10	20–30	40

*Not recommended by the author; *see* Chapter 2, Controversies.

a. Creatinine clearance of 30–50 mL/min, half the average dose per 24 h.
b. Creatinine clearance less than 30 mL/min, half the usual dose every 48 h.

The **oral doses** of commonly used beta-blockers are given in Table 1-4. The **intravenous (IV) doses** are as follows:

Esmolol: 3–6 mg over 1 min, then 1–5 mg/min.
Propranolol: up to 1 mg, at a rate of 0.5 mg/min, repeated if necessary at 2–5-min intervals to a maximum of 5 mg (rarely 10 mg): 0.1 mg/kg.
Metoprolol: up to 5 mg, at a rate of 1 mg/min, repeated if necessary at 5-min intervals to a maximum of 10 mg (rarely 15 mg).
Atenolol: up to 2.5 mg, at a rate of 1 mg/min, repeated if necessary at 5-min intervals to a maximum of 10 mg.
By IV infusion (atenolol): 150 mg/kg over 20 min repeated every 12 h if required.

PHARMACOLOGIC PROPERTIES AND CLINICAL IMPLICATIONS

A clinically useful classification of beta-blockers is given in Figure 1-2, and their pharmacologic properties are summarized in Table 1-5.

Cardioselectivity

Cardioselectivity implies that the drug blocks chiefly the $beta_1$-receptors and therefore partially spares $beta_2$-receptors in the lungs and blood vessels. A small quantity of $beta_1$-receptors is present in the lungs. Large doses of all beta-blocking drugs block $beta_2$-receptors. Selectivity holds only for small doses and may be lost at the doses necessary for the relief of angina or for the control of hypertension. Atenolol, betaxolol, bisoprolol, metoprolol, bevantolol, esmolol, and, to a lesser degree, acebutolol, have less of a blocking effect on $beta_2$-receptors in the lungs, so they are not cardiospecific. They can precipitate bronchospasm in susceptible individuals. Nebivolol is the most $beta_1$-selective, followed by bisoprolol, which is highly selective; the others are moderately to weakly selective.

1. **Bronchospasm.** Cardioselective agents may precipitate bronchospasm in a susceptible patient, and this is no different from that of nonselective drugs, **except** when bronchospasm

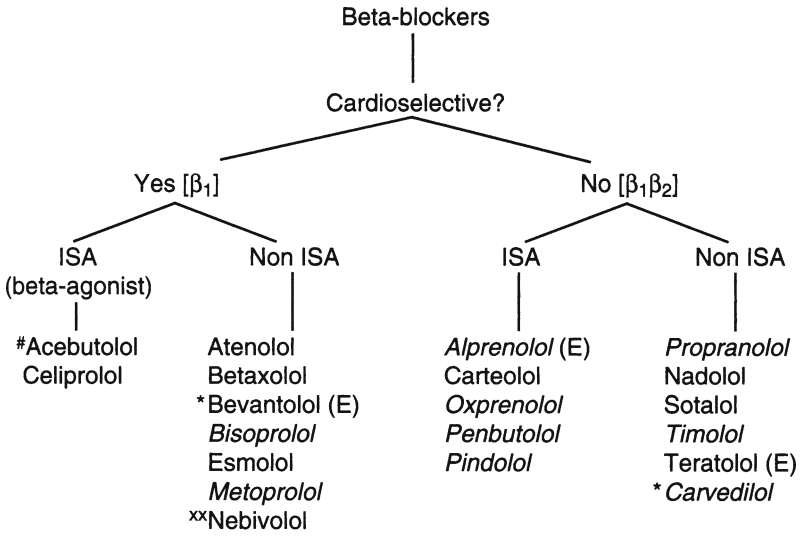

Fig. 1-2. Classification of beta-blockers.

occurs the patient will **respond to a beta$_2$-stimulant** such as albuterol (salbutamol) if a cardioselective drug was administered. When bronchospasm occurs with the use of nonselective drugs, including pindolol, the spasm may be more resistant to beta-stimulants. Beta-blockers should not be given to patients with **bronchial asthma** or severe chronic bronchitis or emphysema. It is wise in such patients to choose alternative therapeutic agents. *Mild chronic bronchitis* is indicated by the following:

- Forced expiratory volume greater than 1.5 L.
- No hospital emergency room or office treatments for bronchospastic disease.

If a patient with mild chronic bronchitis requires treatment with a beta-blocker for angina, treatment should begin with bisoprolol or metoprolol. If bronchospasm occurs, albuterol (salbutamol) should be added, or the beta-blocker should be discontinued. Bisoprolol is the most cardioselective beta-blocker available and is safer than metoprolol for patients with chronic obstructive pulmonary disease (COPD). In humans, the drug has a twofold higher beta$_1$-selectivity than atenolol.

2. **Peripheral vascular disease** (PVD). If a beta-blocker is necessary in a patient with PVD, some clinical trials indicate that it is safer to use a cardioselective drug, atenolol or metoprolol; agents such as carvedilol or bucindolol that cause vasodilation may have a role. Analysis of 11 randomized trials of beta-blockers in patients with PVD showed no worsening of intermittent claudication. Patients with PVD are at high risk for CHD events, and beta-blockers are recommended for all indications. In the United Kingdom Prospective Diabetes Study Group (UKPDS) *(19), atenolol did not worsen PVD, and there was a nonsignificant 48% excess of amputations in the captopril group.*

Table 1-5
Pharmacologic Properties of Beta-Adrenoceptor Blockers

Beta-blocker	*Propranol*	*Timolol*	*Metoprolol*	*Nadolol*	*Atenolol*	*Carvedilol*	*Bisoprolol*	*Acebutolol*	*Sotalol*
Equivalent dose (mg)	80	10	100	60	50	12.5	10	400	80
Potency ratio	1	6–8	1	1–1.5	1–2	?		0.3	0.5–1
Relative			Yes		Yes			Yes	No
cardioselectivity	No	No	Moderate	No	Strong	No	Strong	Mild	
Partial agonist activity (ISA)	0	0	0	0	0	0	Nil	Mild	0
Half life (h)	2–6	2–6	2–6	14–24	7–20		14	2–6	7–20
Variation in plasma level	20-fold	7-fold	7-fold	7-fold	4-fold			?	4-fold
Lipid solubility	Strong	Moderate	Strong	Nil	Nil	Moderate	Moderate	Weak	Nil
Absorption (%)	90	90	95	30	50			75	90
Bioavailability (%)	30	75	50	30	50			40	90
Hepatic metabolism (HM)	HM	60% HM	HM	No	No	HM	50%	HM	No
Renal excretion (RE)		40% RE		RE	RE		50% RE	60% RE	RE

ISA, intrinsic sympathomimetic activity.

3. **Hypoglycemia** stimulates an increase in catecholamine release, which increases blood glucose. The recovery from hypoglycemia may be delayed by nonselective beta-blockers. The incidence of hypoglycemia is higher in insulin-dependent diabetic patients treated with nonselective beta-blockers, whereas both selective and nonselective varieties modify the symptoms of hypoglycemia (with the exception of sweating). Glycolysis and lipolysis in skeletal muscles are mediated mainly by $beta_2$-receptors. Hypoglycemia induced by exercise is more likely to occur with a nonselective beta-blocker. However, evidence to support a greater benefit of selective beta-blockers in joggers is lacking *(20)*. **Insulin** secretion is probably $beta_2$-mediated. Glucose-sulfonylurea-stimulated insulin secretion is inhibited by beta-blockers. Beta-blockers may increase blood glucose by 1.0–1.5 mmol/L, but this glucose intolerance is not type 2 diabetes.

The following points deserve consideration:

- Catecholamine stimulation of $beta_2$-receptors produces transient hypokalemia. Thus, cardioselective drugs that spare $beta_2$-receptors may fail to maintain constancy of serum potassium in response to increase in epinephrine and norepinephrine during acute MI *(21)*.
- *Noncardioselective agents are superior to selective agents in preventing fluctuations of serum potassium concentration during stress and possibly during acute MI.*
- *Nonselective drugs should confer a greater degree of cardioprotection; carvedilol, propranolol, and timolol have been shown to prevent total mortality and cardiac death in well-controlled RCTs.*
- *Carvedilol, therefore should replace the commonly used metoprolol in patients with acute MI and in heart failure patients post-MI.*

Intrinsic Sympathomimetic Activity (ISA)

ISA indicates partial agonist activity, the primary agonists being epinephrine and isoproterenol. Beta-blockers that cause a small agonist response (i.e., stimulate as well as block the beta-receptors) include pindolol, alprenolol, acebutolol, celiprolol, carteolol, oxprenolol, and practolol. The last drug has been removed from medical practice because it produced the oculomucocutaneous syndrome. Beta-blockers with ISA cause a slightly lower incidence of bradycardia compared with non-ISA drugs. In practice, this is a minor advantage in the choice of a beta-blocker. The heart rate at rest may be only slightly lowered or unchanged; in patients with angina, a slower heart rate is conducive to less pain on activity.

The RPP at rest is not significantly reduced. Myocardial oxygen consumption is therefore not usually reduced at rest by ISA beta-blockers. Beta-blockers with ISA, therefore, carry **no advantage** in angina at rest or in angina occurring at low exercise levels; in particular, they do not have a beneficial effect on cardioprotection. The ISA of beta-blockers produces adverse effects on ventricular fibrillation (VF) threshold *(22)*. Acebutolol with weak ISA, however, has been shown to prevent cardiac death. Because they limit exercise tachycardia, these drugs do have a **minor role** to play in the treatment of patients who have a relatively low resting heart rate (50–60/min) and in whom further bradycardia may not be acceptable. Even in this subgroup, it is still important to exclude patients with sick sinus syndrome because all beta-blockers are contraindicated here. **Renin** secretion may remain unaltered or may even be increased by agents with ISA. There may be added sodium and water retention, causing edema. There is no clear-cut evidence that peripheral vascular complications are less frequent when beta-blockers with partial agonist activity are used. *Agents with ISA, except acebutolol (very weak ISA) are not recommended by the author because of the aforementioned points; these are not CP drugs.*

Membrane-Stabilizing Activity

The quinidine-like or local anesthetic action, membrane-stabilizing activity (MSA), is of no clinical importance, except perhaps for its effect on platelets and in the treatment of glaucoma. It is not related to the antiarrhythmic, antianginal, or CP properties of beta-blockers. Unlike most available beta-blockers, timolol and betaxolol have no MSA. Because of high potency and lack of anesthetic effect, these drugs are the only beta-blockers that have been proved safe and effective in the treatment of glaucoma when used topically.

MSA appears to be important in the management of thyrotoxic crisis, and propranolol has been shown to be more effective than nadolol in this condition.

Effects on Renin

Renin release from the juxtaglomerular cells is suppressed by $beta_1$-receptor blockade; this results in reduced activity of the renin-angiotensin system. Beta-blockers enhance the lifesaving effects of ACE inhibitors in patients with HF or MI *(23)*.

Lipid Solubility

- Highly lipid-soluble, lipophilic beta-blockers—carvedilol, propranolol, timolol, and metoprolol—reach high concentrations in the brain and are metabolized in the liver.
- Atenolol, nadolol, and sotalol are lipid insoluble, show poor brain concentration, and are not metabolized by the liver; they are water soluble, are excreted by the kidneys, and have a long half-life. Pindolol and timolol are about 50% metabolized and about 50% excreted by the kidney.
- Brain:plasma ratios are 15:1 for propranolol, 3:1 for metoprolol, and 1:8 for atenolol.
- Lipid-insoluble, hydrophilic beta-blockers appear to have a lower incidence of central nervous system (CNS) side effects such as vivid dreams, significant effects on sleep *(24)*, impairment of very fast mental reactions *(25)*, depression, fatigue, and impotence. Depending on dosage, even the lipid-insoluble drugs can achieve sufficient brain concentration to impair very fast mental reactions. There is little doubt, however, that atenolol causes fewer central side effects than propranolol *(25)*. Timolol has been shown to cause less bizarre dreams than pindolol or propranolol in small groups of patients.
- **Lipid-soluble beta-blocking agents with high brain concentrations block sympathetic discharge in the hypothalamus better than water-soluble agents *(26)*, and they are more effective in the prevention of cardiac deaths.**
- Bisoprolol is 50% lipophilic and liver metabolized but does not involve the cytochrome P-450 3A4 pathway; renal elimination is approx 50%.

Plasma Volume

A reduction in cardiac output is usually followed by an increase in plasma volume. Beta-blockers cause a reduction in plasma volume; the exact reason for this is unknown. Pindolol (ISA) may increase plasma volume.

Hepatic Metabolism

Propranolol, oxprenolol, and metoprolol have high first-pass liver metabolism. Timolol and acebutolol have modest lipid solubility and undergo major hepatic metabolism. Acebutolol is metabolized to an active metabolite, diacetolol, which is water soluble and is excreted by the kidneys. Atenolol, nadolol, and sotalol are not metabolized in the liver. First-pass metabolism varies greatly among patients and can alter the dose of drug required, especially with propranolol. Cigarette smoking interferes with drug metabolism in the

liver and reduces the efficacy of propranolol, other hepatically metabolized beta-blockers, and calcium antagonists *(27)*.

Effects on Blood and Arteries

1. **Platelets.** Platelet hyperaggregation seen in patients with angina or induced by catecholamines can be normalized by propranolol. The second stage of platelet aggregation, induced by adenosine diphosphate, catecholamines, collagen, or thrombin, can be abolished or inhibited by propranolol. Propranolol is able to block [^{14}C]serotonin released from platelets and inhibits platelet adherence to collagen; these favorable effects can be detected with the usual clinical doses of propranolol and other beta-blocking drugs.
2. **HDL-C.** It has been suggested that beta-blockers may increase atherosclerosis by decreasing HDL levels. Propranolol causes a mild decrease in HDL levels of approx 7%. There is at present no proof that decreasing HDL values from, for example, 55 to 50 mg/dL (i.e., from 1.4 to 1.3 mmol/L), will have any adverse effect on the progression of atherosclerosis. Some studies suggest that HDL_2 remains unaltered *(28,29)*. There is little doubt that in some patients HDL_2 is slightly lowered. In one study, there was an 8% lowering of HDL_2 and a rise in triglycerides produced by both propranolol and pindolol at 6 wk. Beta-blockers do not decrease total serum cholesterol. The effect of beta-blockers on triglycerides is variable, and the evidence associating raised triglycerides with ischemic heart disease (IHD) is weak. Acebutolol with weak ISA causes no significant disturbance of lipid levels. **Bisoprolol**, being highly $beta_1$-selective, does not significantly decrease HDL-C.
3. **Arteries.** Beta-blockers decrease the force and velocity of cardiac contraction, decrease, RPP and heart rate × peak velocity, and therefore decrease hemodynamic stress on the arterial wall, especially at the branching of arteries. This action may decrease the atherosclerotic process and *plaque rupture*. This beneficial hemodynamic effect, and that described on blood coagulation, may favorably influence atherosclerotic CHD and subsequent occlusion by platelets or thrombosis.
4. **Coronary blood flow.** Beta-blockers increase diastolic coronary perfusion time and coronary blood flow because bradycardia lengthens the diastolic filling time. Thus, these agents produce beneficial effects in angina and IHD by increasing coronary blood supply while reducing myocardial oxygen demands; the reduction of hydraulic stress in the coronary arteries appears to *provide protection from plaque fissuring and rupture* (*see* Fig. 1-1).

Effect on Serum Potassium

- Beta-blockade causes a mild increase in serum potassium because of blockade of the $beta_2$-mediated epinephrine activation of the Na^+, K^+-ATPase pump, which transports potassium from extracellular fluid into cells.
- During stress, serum potassium has been observed to decrease up to 1.0 mEq (mmol)/L; this fall in serum potassium concentration can be prevented by blockade of $beta_2$-receptors.
- *Noncardioselective agents are superior to selective agents in preventing fluctuations of serum potassium concentration during stress and possibly during acute MI.*

SALUTARY EFFECTS OF BETA-ADRENERGIC BLOCKADE

These beneficial effects *(30)* are outlined in Fig. 1-1 and include the following:

- A decrease in heart rate increases the diastolic interval and allows for improved diastolic filling of the coronary arteries. This effect is especially important during exercise in patients with angina.

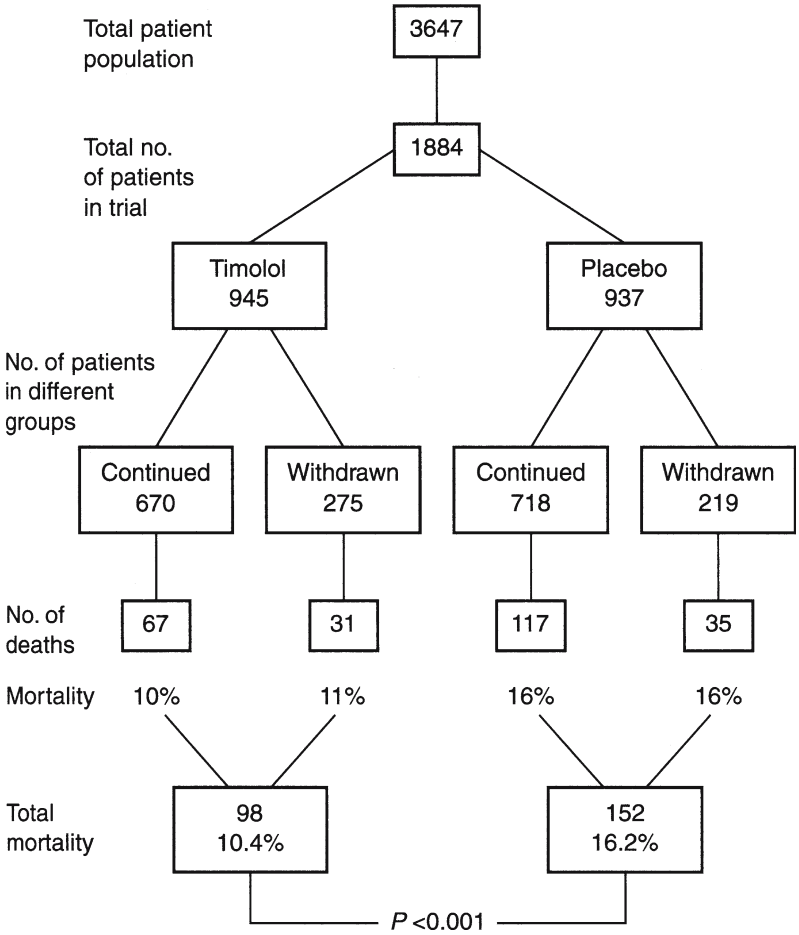

Fig. 1-3. Results of the Norwegian Multicenter Postinfarction Trial of timolol. Timolol was administered at a dosage of 10 mg twice daily from 7 to 28 d. Patients were followed for a mean duration of 17 mo. The age range was 20 to 75 yr. (From Am J Cardiol 1990;66:4C; with permission of Excerpta Medica, Inc. [Elsevier].)

- The RPP is decreased, so there is less myocardial demand for oxygen, resulting in an improvement of ischemia.
- A decrease in sudden cardiac death has been documented in several studies. *An impressive 67% reduction in sudden death was observed in smokers and nonsmokers in the Timolol Norwegian Reinfarction Study (16)*: timolol decreased the overall mortality rate by 36%, $p < 0.001$ (Fig. 1-3).
- This beneficial effect of beta-blockers in postinfarction patients was reconfirmed in the Beta-Blocker Heart Attack Trial (BHAT) *(31)*. This well-run trial randomized 16,400 post-MI patients to propranolol or placebo and after 2-yr follow-up showed a 26% reduction in the mortality rate with propranolol *(31)*.
- A decrease in fatal arrhythmias and an increase in VF threshold, as well as amelioration of bothersome benign ventricular and supraventricular arrhythmias, have been established by several clinical studies.
- A decrease in the velocity and force of myocardial contraction results in a decrease in myocardial oxygen requirement and also reduces the rate of rise of aortic pressure, which is

important in the prevention and treatment of aortic dissection. Beta-blockade is effective in slowing the rate of aortic dilation and reducing the development of aortic complications in patients with Marfan's syndrome *(32)*.

- A decrease in ejection velocity reduces hydraulic stress on the arterial wall that could be crucial at the site of atheroma. This mechanism of action may reduce the incidence of plaque rupture and may thus protect patients from coronary thrombosis and fatal or nonfatal infarction *(31)*.
- Beta-blockers may prevent early morning platelet aggregation induced by catecholamines and may decrease the early morning peak incidence of acute MI *(33)*.
- Low heart rate variability predicts mortality in postinfarction patients *(34,35)*. Metoprolol and atenolol enhance heart rate variability in patients with CHD *(36)*.

The favorable effect of beta-blockade on sudden death relative to reduction in heart rate is observed only with the use of beta-blockers that reduce heart rate *(37,38)*. Beta-blockers such as pindolol with marked ISA and no bradycardic response at rest cause no reduction in sudden death or mortality rates Acebutolol with mild ISA, however, caused a 48% reduction in overall mortality rate and a 58% reduction in cardiovascular mortality rate in postinfarction patients *(39)*.

BETA-BLOCKERS VERSUS CALCIUM ANTAGONISTS AND ORAL NITRATES

The clinical effects of beta-blockers compared with calcium antagonists and oral nitrates are shown in Table 1-1.

1. **A decrease in heart rate** by beta-blockers allows for a **longer diastolic filling** time and therefore **greater coronary perfusion**.
2. It is often stated that beta-blockers may decrease coronary blood flow, but this is secondary to the reduction in myocardial work; in practice, this effect is not harmful. A decrease in blood flow does not occur if there is ischemia, and therefore it is not of importance in occlusive coronary disease. If you need less oxygen, you will need less blood flow; this fact is often misinterpreted. The RPP at rest and on maximal exercise is reduced by beta-blockers, but it is not decreased by calcium antagonists or oral nitrates.
3. Both beta-blockers and calcium antagonists have been proved to be more effective than nitrates when they are used alone in the relief of angina pectoris.
4. In animals, **blood flow** to the subendocardial ischemic myocardium distal to an organic obstruction is improved by beta-blockers, and it may be decreased by calcium antagonists *(40)*. Beta-blockers divert blood from the epicardium to the ischemic subendocardium by activation of autoregulatory mechanisms. Calcium antagonists may have the opposite effect and can cause deterioration in patients with critical coronary artery stenosis *(41)*. Unfortunately, calcium antagonists, when used without a beta-blocker in patients with unstable angina, can increase chest pain and infarction, and they appeared to increase mortality in the largest subgroup of patients with unstable angina. Oral nitrates have an effect similar to that of calcium antagonists.
5. Beta-blockers can prevent **recurrent VF** in animals and in patients *(42–44)*, whereas calcium antagonists do not significantly alter VF threshold.
6. Beta-blockers have been shown to prevent cardiac death in patients after MI, followed for 2 yr *(16,31,39)*. There is no reason to suppose that the same favorable effect is absent in the patient with angina pectoris or hypertension, provided an appropriate beta-blocker is used at CP doses (metoprolol, timolol, or propranolol, the last drug in nonsmokers). In

contrast, calcium antagonists provide only symptomatic relief. There are good reasons, therefore, for employing beta-blockers as first-line drugs in the treatment of **angina pectoris**, and this should remain the case until other therapeutic maneuvers are proved conclusively to prevent sudden and other cardiac deaths. Current evidence clearly indicates that calcium antagonists do not prevent cardiac deaths. *There has been a misguided tendency to replace beta-blockers in the management of angina pectoris with calcium antagonists because they are just as effective for the relief of cardiac pain in patients with angina pectoris. Calcium antagonists cannot be regarded as alternative therapy; they constitute suitable therapy when beta-blockers are contraindicated.*

7. Occasionally, **CAS** can be made worse in allowing unopposed alpha-vasoconstriction. It is emphasized that variant angina resulting from CAS is rare, and only the occasional patient may have an increase in chest pain secondary to beta-blockers *(40,45)*. Usually, this is not dangerous, and it gives an indication that CAS may be present. In patients in whom the mechanism of unstable angina is unclear, beta-blockers should be used combined with calcium antagonists or nitrates *(45)*.

INDICATIONS FOR BETA-BLOCKERS

Angina

The use of beta-blockers in the management of angina pectoris and silent ischemia is discussed in Chapter 10 (*see* Table 1-3).

Arrhythmias

- Ventricular premature beats that are symptomatic in patients with normal hearts and in those with a history of cardiac disease benefit from treatment with a beta-blocker. In the acute phase of MI, ventricular premature beats and ischemia caused by catecholamine surge respond favorably.
- AV nodal reentrant tachycardia may be aborted by beta-blocker therapy.
- Atrial fibrillation: rate control is best achieved with a small dose of a beta-blocking drug, particularly because digoxin does not decrease heart rate adequately in patients during exercise. Sotalol may decrease the recurrence of paroxysmal atrial fibrillation. Other beta-blockers do not possess class III activity and are not recommended for the maintenance of sinus rhythm in patients with paroxysmal atrial fibrillation. In patients converted to sinus rhythm by DC shock, maintenance of sinus rhythm with the use of sotalol is as good as quinidine.
- Esmolol IV may be used instead of diltiazem or verapamil, particularly in the perioperative period for most supraventricular tachycardias (SVTs) including atrial fibrillation.
- Nonsustained ventricular tachycardia (VT) is more appropriately treated with a beta-blocker than with antiarrhythmic agents. The use of most antiarrhythmics has dwindled because of the increased mortality attributed to these agents.
- Recurrent episodes of VT may be prevented in some patients. In the management of life-threatening arrhythmias in patients after cardiac arrest, metoprolol has been shown to be as good as amiodarone. When amiodarone and a beta-blocker combination is used, it appears that the prolongation of life observed is caused mainly by the addition of the beta-blocker. A European trial has shown that empiric use of metoprolol was as effective as electrophysiologically guided antiarrhythmic therapy *(46)*. Sotalol has been shown to be more effective than class I antiarrhythmics for VT. In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), all the good effects observed were in patients taking a beta-blocker along with amiodarone.

- Recurrent VF is unique among cardiac arrhythmias because the management is immediate countershock. Antifibrillatory drugs can be useful in the prevention of recurrent VF. Beta-blockers have long been known to have a role in the management of patients with persistently recurring VF *(42,43)*. Beta-blockers decrease the incidence of VF in patients with acute MI *(44)*. Beta-blockers increase VF threshold and should be given by the IV route in patients with recurrent VF if lidocaine or bretylium fails. IV beta-blockers are given by some before the use of bretylium.
- The importance of beta-blockade in the management of patients with sustained VT has been demonstrated in a prospective study *(47)*.

Hypertension

- **Young patients.** A beta-blocker is the drug of choice in younger and older white patients with or without comorbid conditions, particularly IHD, MI, diabetes, and hyperlipidemia. Beta-blockers are generally known to be effective in white people aged less than 65 yr. In a study by Matterson and colleagues *(48)* in African-American patients younger than 60 yr, atenolol was, surprisingly, the second most effective drug, after diltiazem, and it was more effective than hydrochlorothiazide (HCTZ). *See* treatment algorithms in Chapter 9, Hypertension Controversies.
- **Elderly patients.** *Contrary to common opinion, beta-blockers have been proved effective in older white patients (48).* The statement that beta-blockers are not advisable in elderly hypertensive patients, as given in textbooks and excellent editorials, review articles *(1)*, and JNC and WHO guidelines, is **false because it is based on the results of the Medical Research Council (MRC) trial in the elderly** *(49)* (*see* Chapters 8 and 9). Unfortunately, of the 4396 elderly hypertensive patients in this trial, 25% were lost to follow-up, and the 63% randomized to a beta-blocker either withdrew or were lost to follow-up. More than half the patients were not taking their assigned therapy by the end of the study. Cruickshank's review *(1)* quotes these relevant statistics and yet states "certainly beta-blockers should not be first-line therapy for elderly hypertensives." *The misleading MRC trial rings out this statement: elderly hypertensive patients respond best to diuretic-based rather than beta-blocker-based therapy in terms of fewer heart attacks.* If this poorly conducted MRC trial carries so much credibility, then diuretics should be used instead of beta-blockers to prevent heart attacks in all cardiac patients (hypertensive and normotensive) with high risk for CHD events. However, every practitioner knows that diuretics are not prescribed for prevention of CHD events in patients at risk for CHD events. Why prescribe them in place of beta-blockers in elderly hypertensive patients based on one unsound RCT? In the HANE (HCTZ, atenolol, nitrendipine, enalapril) study *(50)*, at 8 wk the blood pressure response rate was significantly higher for atenolol (64%) than for enalapril (50%), HCTZ (46%), or nitrendipine (45%). Effectivity was maintained at the end of 1 yr. **A beta-blocker was as effective in elderly patients as in younger ones**.
- In patients with hypertension or angina with LV dysfunction, a beta-blocker used in combination with an ACE inhibitor improves outcome.
- For prevention and regression of LVH, a beta-blocker or ACE inhibitor is more effective than a diuretic or calcium antagonist *(23,51)*.

Acute Myocardial Infarction

For the **first 7 d**, beta-blockers given within 4 h of an acute MI slightly reduce the 7-d mortality rate. There is evidence that beta-blockers can lower the incidence of acute MI, decrease the size of infarction, reduce the incidence of VF, and reduce the incidence of early cardiac rupture. Reduction of infarct size has been documented with the early use of

timolol in acute MI *(52)*. Beta-blockers are recommended from d 1 and for 2 yr or more; their combination with ACE inhibitors is superior to ACE inhibitors alone *(23)*. During this period, these agents prevent sudden death and nonfatal and fatal MI and reduce overall mortality.

In the **CAPRICORN** study *(53)*, carvedilol produced an outstanding reduction in cardiac deaths and events in early post-MI patients (*see* the discussion of study results in Chapter 22).

- Caution is needed because beta-blockers may increase cardiac mortality when used indiscriminately in patients in whom the drugs are contraindicated, particularly IV use in patients who are hemodynamically unstable, with impending cardiogenic shock, pulmonary edema, or acute MI with HF (*see* COMMIT, Chapter 22).

Heart Failure

The potentially deleterious effects of overactivation of the sympathetic nervous system in HF are now well established; beta-blockers curb this sympathetic overactivation, hence the rationale for the judicious use of titrated doses of beta-blockers in patients with impaired LV function (*see* Chapter 12 for a discussion of the Second Cardiac Insufficiency Bisoprolol Study [CIBIS II] *(54)* and COPERNICUS *(55)*, which showed a significant reduction in overall mortality with bisoprolol and carvedilol therapy).

- Carvedilol has been shown in an RCT in patients with class II–III HF to decrease mortality and the risk of hospitalization for recurrent HF. Thus, approved beta-blockers have a new indication for the management of patients with LV dysfunction or class I–III HF.
- In **COPERNICUS** *(55)*, carvedilol produced a significant reduction in serious events in patients with compensated class IV HF, and the indication has been extended from class I to *compensated class IV* patients (*see* Chapters 12 and 22).
- *Most important, in MERIT-HF (56), only a small dose of a beta-blocking drug administered to patients in the low-dose subgroup achieved risk reduction similar to that observed in the high-dose subgroup.*

Elective Percutaneous Coronary Intervention (PCI)

Beta-blocker therapy is associated with a marked long-term survival benefit among patients undergoing successful PCI *(57)*; beta-blocker therapy was associated with a reduction from 6.0% to 3.9% at 1 yr ($p = 0.0014$).

Prolonged QT Interval Syndromes

- Congenital syndromes are rare, but they do respond to beta-blockers. These agents appear to restore an imbalance between the left and right stellate ganglia. If recurrent episodes of torsades de pointes develop in a patient with a prolonged QT interval, the condition usually responds to propranolol and acutely to pacing. Propranolol has been proved to be useful in the congenital long-QT syndromes (*see* Chapter 14).
- Beta-blockers have a variable effect in the acquired idiopathic long-QT syndromes.

Dissecting Aneurysm

A beta-blocker is the drug of choice to reduce the rate of rise of aortic pressure, which increases dissection. Even if the systolic blood pressure is 100–120 mmHg, propranolol or another IV preparation should be commenced. If the blood pressure exceeds 130 mmHg, a careful infusion of nitroprusside, or trimethaphan along with furosemide, is given to