1 – β-blocking agents

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> *"The β-adrenergic-G-protein-adenylyl cyclase system is the most powerful mechanism to augment human cardiac performance. Chronic desensitization in heart failure must impair and weaken cardiac performance."*
>
> *Brodde, 2007[1]*

β-adrenergic receptor antagonist agents retain their dominant position in the therapy of all stages of ischemic heart disease, with the exception of Prinzmetal's vasospastic variant angina. β-blockade is still regarded as standard therapy for effort, mixed effort, rest, and unstable angina. β-blockers reduce mortality in the long term after myocardial infarction (MI), and exert a markedly beneficial effect on outcomes in patients with chronic congestive heart failure (CHF). β-blockers are antiarrhythmic agents and standard therapy to control the ventricular rate in chronic atrial fibrillation. Conversely, established approved indications in the United States (Table 1-1) include some examples of conditions such as hypertension for which β-blockade used to be, but no longer is, clear-cut "first-line" therapy. When correctly used, β-blockers are relatively safe. In older adults β-blockade risks include excess nodal inhibition and a decreased cardiac output, which in the senescent heart could more readily precipitate heart failure.

The extraordinary complexity of the β-adrenergic signaling system probably evolved millions of years ago when rapid activation was required for hunting and resisting animals, with the need for rapid inactivation during the period of rest recovery. These mechanisms are now analyzed.[2]

Table 1-1   -- Indications For β-Blockade and US FDA-Approved Drugs

Indications for β-Blockade	FDA-Approved Drugs
1. Ischemic Heart Disease	
Angina pectoris	Atenolol, metoprolol, nadolol, propranolol
Silent ischemia	None
AMI, early phase	Atenolol, metoprolol
AMI, follow-up	Propranolol, timolol, metoprolol, carvedilol
Perioperative ischemia	Bisoprolol,* atenolol*
2. Hypertension	
Hypertension, systemic	Acebutolol, atenolol, bisoprolol, labetalol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol
Hypertension, severe, urgent	Labetalol
Hypertension with LVH	Prefer ARB
Hypertension, isolated systolic	No outcome studies, prefer diuretic, CCB
Pheochromocytoma (already receiving alpha-blockade)	Propranolol
Hypertension, severe perioperative	Esmolol
3. Arrhythmias	
Excess urgent sinus tachycardia	Esmolol
Tachycardias (sinus, SVT, and VT)	Propranolol
Supraventricular, perioperative	Esmolol

| Indications for β-Blockade	FDA-Approved Drugs
Recurrences of Afib, Afl	Sotalol
Control of ventricular rate in Afib, Afl	Propranolol
Digitalis-induced tachyarrhythmias	Propranolol
Anesthetic arrhythmias	Propranolol
PVC control	Acebutolol, propranolol
Serious ventricular tachycardia	Sotalol
4. Congestive heart failure	Carvedilol, metoprolol, bisoprolol*
5. Cardiomyopathy	
Hypertrophic obstructive cardiomyopathy	Propranolol
6. Other cardiovascular indications	
POTS	Propranolol low dose*
Aortic dissection, Marfan syndrome, mitral valve prolapse, congenital QT prolongation, tetralogy of Fallot, fetal tachycardia	All?* Only some tested*
7. Central indications	
Anxiety	Propranolol*
Essential tremor	Propranolol
Migraine prophylaxis	Propranolol, nadolol, timolol
Alcohol withdrawal	Propranolol,* atenolol*
8. Endocrine	
Thyrotoxicosis (arrhythmias)	Propranolol
9. Gastrointestinal	
Esophageal varices? (data not good)	Propranolol?* Timolol negative study*
10. Glaucoma (local use)	Timolol, betoxalol, carteolol, levobunolol, metipranolol

Afib, Atrial fibrillation; *Afl,* atrial flutter; *AMI,* acute myocardial infarction; *ARB,* angiotensin receptor blocker; *CCB,* calcium channel blocker; *FDA,* Food and Drug Administration; *LVH,* left ventricular hypertrophy; *POTS,* postural tachycardia syndrome; *PVC,* premature ventricular contraction; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.

*Well tested but not FDA approved.

Mechanism

The β1-adrenoceptor and signal transduction.

Situated on the cardiac sarcolemma, the β1-receptor is part of the adenylyl (= adenyl) cyclase system (Fig. 1-1) and is one of the group of G protein–coupled receptors. The G protein system links the receptor to adenylyl cyclase (AC) when the G protein is in the stimulatory configuration (G_s, also called $G\alpha s$). The link is interrupted by the inhibitory form (G_i or $G\alpha i$), the formation of which results from muscarinic stimulation following vagal activation. When activated, AC produces cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). The intracellular second messenger of β1-stimulation is cAMP; among its actions is the "opening" of calcium channels to increase the rate and force of myocardial contraction (the positive inotropic effect) and increased reuptake of cytosolic calcium into the sarcoplasmic reticulum (SR; relaxing or lusitropic effect, see Fig 1-1). In the sinus node the pacemaker current is increased (positive chronotropic effect), and the rate of conduction is accelerated (positive dromotropic effect). The effect of a given β-blocking agent depends on the way it is absorbed, the binding to plasma proteins, the generation of metabolites, and the extent to which it inhibits the β-receptor (lock-and-key fit).
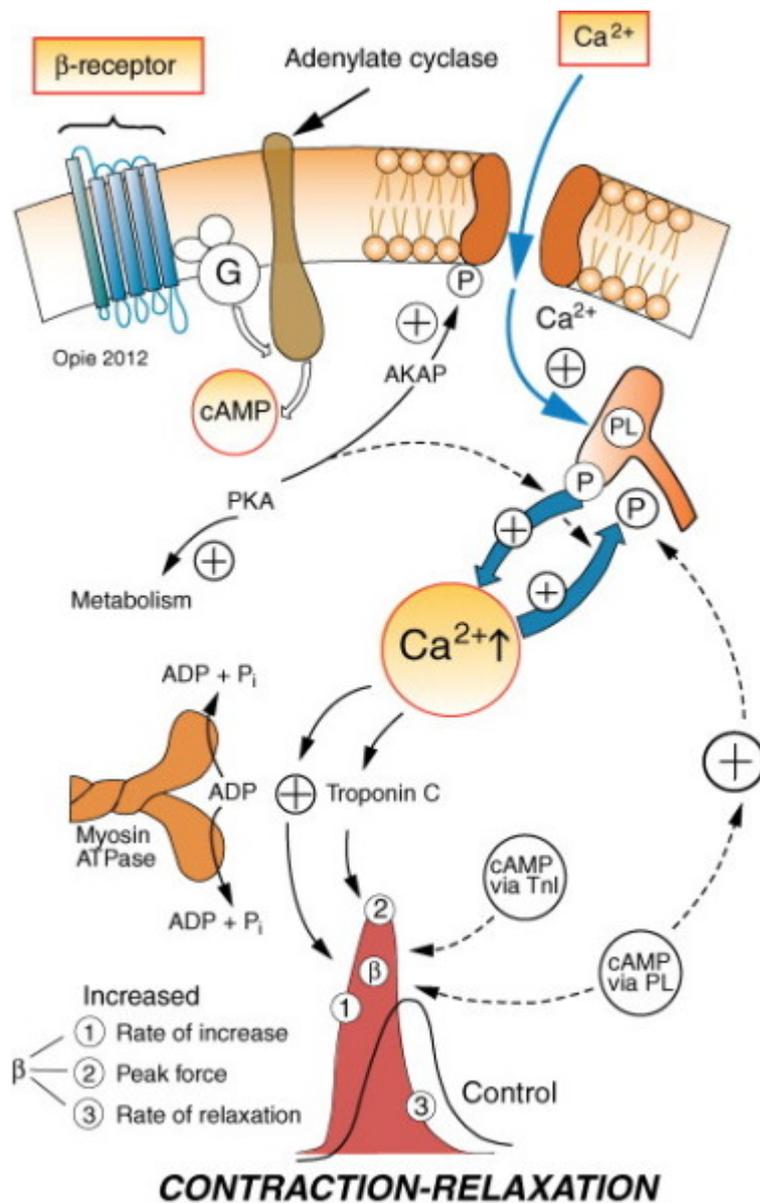
Figure 1-1 β-adrenergic signal systems involved in positive inotropic and lusitropic (enhanced relaxation) effects. These can be explained in terms of changes in the cardiac calcium cycle. When the β-adrenergic agonist interacts with the β-receptor, a series of G protein-mediated changes lead to activation of adenylate cyclase and formation of the adrenergic second messenger, cyclic adenosine monophosphate (cAMP). The latter acts via protein kinase A to stimulate metabolism and to phosphorylate (P) the calcium channel protein, thus increasing the opening probability of this channel. More Ca^{2+} ions enter through the sarcolemmal channel, to release more Ca^{2+} ions from the sarcoplasmic reticulum (SR). Thus the cytosolic Ca^{2+} ions also increase the rate of breakdown of adenosine triphosphate (ATP) and to adenosine diphosphate (ADP) and inorganic phosphate (P_i). Enhanced myosin adenosine triphosphatase (ATPase) activity explains the increased rate of contraction, with increased activation of troponin-C explaining increased peak force development. An increased rate of relaxation (lusitropic effect) follows from phosphorylation of the protein phospholamban (PL), situated on the membrane of the SR, that controls the rate of calcium uptake into the SR.
(Figure © L. H. Opie, 2012.)

β₂-receptors.

The β-receptors classically are divided into the β₁-receptors found in heart muscle and the β₂-receptors of bronchial and vascular smooth muscle. If the β-blocking drug selectively interacts better with the β₁- than the β₂-receptors, then such a *β₁-selective blocker* is less likely to interact with the β₂-receptors in the bronchial tree, thereby giving a degree of protection from the tendency of nonselective β-blockers to cause pulmonary complications. There are sizable populations, approximately 20% to 25%, of β₂-receptors in the

myocardium, with relative upregulation to approximately 50% in heart failure. Various "anti-cAMP" β_1-receptor–mediated effects (see later in this chapter) could physiologically help to limit the adverse effects of excess β_1-receptor catecholamine stimulation. Other mechanisms also decrease production of β_2-mediated production of cAMP in the local microdomain close to the receptor.[3] These mechanisms to limit cAMP effects could, however, be harmful in heart failure in which β-induced turn-off mechanisms already inhibit the activity of cAMP (next section).

β-stimulation turn-off.

β-receptor stimulation also invokes a "turn-off" mechanism, by activating β-adrenergic receptor kinase (β-ARK now renamed G protein–coupled receptor kinase 2 [GRK_2]), which phosphorylates the receptor that leads to recruitment of β-arrestin that desensitizes the stimulated receptor (see Fig. 1-7). β-arrestin not only mediates desensitization in heart failure, but also acts physiologically as a signal transducer, for example to induce antiapoptotic signaling.[4]

β₃-receptors.

Endothelial β_3-receptors mediate the vasodilation induced by nitric oxide in response to the vasodilating β-blocker nebivolol (see Fig. 1-10).[5],[6]

Secondary effects of β-receptor blockade.

During physiologic β-adrenergic stimulation, the increased contractile activity resulting from the greater and faster rise of cytosolic calcium (Fig. 1-2) is coupled to increased breakdown of ATP by the myosin adenosine triphosphatase (ATPase). The increased rate of relaxation is linked to increased activity of the sarcoplasmic/endoplasmic reticulum calcium uptake pump. Thus the uptake of calcium is enhanced with a more rapid rate of fall of cytosolic calcium, thereby accelerating relaxation. Increased cAMP also increases the phosphorylation of troponin-I, so that the interaction between the myosin heads and actin ends more rapidly. Therefore the β-blocked heart not only beats more slowly by inhibition of the depolarizing currents in the sinoatrial node, but has a decreased force of contraction and decreased rate of relaxation. Metabolically, β-blockade switches the heart from using oxygen-wasting fatty acids toward oxygen-conserving glucose.[7] All these *oxygen-conserving properties* are of special importance in the therapy of ischemic heart disease. Inhibition of lipolysis in adipose tissue explains why gain of body mass may be a side effect of chronic β-blocker therapy.

BETA-RECEPTOR BLOCKADE
Opie 2012
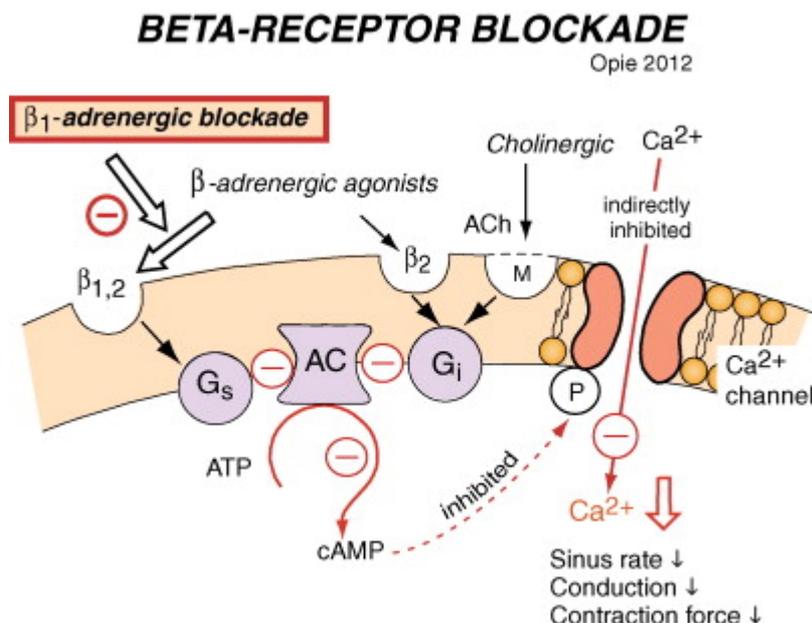
Figure 1-2 **The β-adrenergic receptor** is coupled to adenyl (= adenylyl) cyclase (AC) via the activated stimulatory G-protein, Gs. Consequent formation of the second messenger, cyclic adenosine monophosphate (cAMP) activates protein kinase A (PKA) to phosphorylate (P) the calcium channel to increase calcium ion entry. Activity of adenyl cyclase can be decreased by the inhibitory subunits of the acetylcholine (ACh)–associated inhibitory G-protein, Gi. cAMP is broken down by phosphodiesterase (PDE) so that PDE-inhibitor drugs have a sympathomimetic effect. The PDE is type 3 in contrast to the better known PDE type 5 that is inhibited by sildenafil (see Fig. 2-6). A current hypothesis is that the β_2–receptor stimulation additionally signals via the inhibitory G-protein, Gi, thereby modulating the harm of excess adrenergic activity.
(Figure © L. H. Opie, 2012.)

Receptor downregulation in human heart failure.

Myocardial β-receptors respond to prolonged and excess β-adrenergic stimulation by internalization and downregulation, so that the β-adrenergic inotropic response is diminished. As outlined for β_2-receptors, there is an "endogenous antiadrenergic strategy," self-protective mechanism against the known adverse effects of excess adrenergic stimulation. However, the role of the β_2-receptor is still not fully clarified in advanced heart failure.[8] Regarding the β_1-receptor, the first step in internalization is the increased activity of β_1ARK, now renamed GRK_2 (see Fig. 1-7). GRK_2 then phosphorylates the β_1-receptor, which in the presence of β-arrestin becomes uncoupled from G_s and internalizes. If the β-stimulation is sustained, then the internalized receptors may undergo lysosomal destruction with a true loss of receptor density or downregulation. However, *downregulation* is a term also often loosely applied to any step leading to loss of receptor response.

Clinical β-receptor downregulation occurs during prolonged β-agonist therapy. During continued infusion of dobutamine, a β-agonist, there may be a progressive loss or decrease of therapeutic efficacy, which is termed *tachyphylaxis.* The time taken and the extent of receptor downgrading depend on multiple factors, including the dose and rate of infusion, the age of the patient, and the degree of preexisting downgrading of receptors as a result of CHF. In CHF, the β_1-receptors are downregulated by the high circulating catecholamine levels, so that the response to β_1-stimulation is diminished. Cardiac β_2-receptors, not being downregulated to the same extent, are therefore increased in relative amounts; there are also some defects in the coupling mechanisms. Recent recognition of the dual signal path for the effects of β_2-receptor stimulation leads to the proposal that in CHF continued activity of the β_2-receptors may have beneficial consequences such as protection from programmed cell death or apoptosis. In practice, however, combined $\beta_1\beta_2$-receptor blockade by carvedilol is probably superior in the therapy of heart failure to β_1 selective blockade.

Receptor number upregulation.

During sustained β-blocker therapy, the number of β-receptors increases.[9] This change in the receptor density could explain the striking effect of long-term β-blockade in heart failure, namely improved systolic function, in contrast to the short-term negative inotropic effect. This inotropic effect is not shared by other agents such as the angiotensin-converting enzyme (ACE) inhibitors that reduce mortality in heart failure.

Cardiovascular effects of β-blockade

β-blockers were originally designed by the Nobel prize winner Sir James Black to counteract the adverse cardiac effects of adrenergic stimulation. The latter, he reasoned, increased myocardial oxygen demand and worsened angina. His work led to the design of the prototype β-blocker, *propranolol*. By blocking the cardiac β-receptors, he showed that these agents could induce the now well-known inhibitory effects on the sinus node, atrioventricular (AV) node, and on myocardial contraction. These are respectively the negative chronotropic, dromotropic, and inotropic effects (Fig. 1-3). Of these, it is especially bradycardia and the negative inotropic effects that are relevant to the therapeutic effect in angina pectoris because these changes decrease the myocardial oxygen demand (Fig. 1-4). The inhibitory effect on the AV node is of special relevance in the therapy of supraventricular tachycardias (SVTs; see Chapter 8), or when β-blockade is used to control the ventricular response rate in atrial fibrillation.
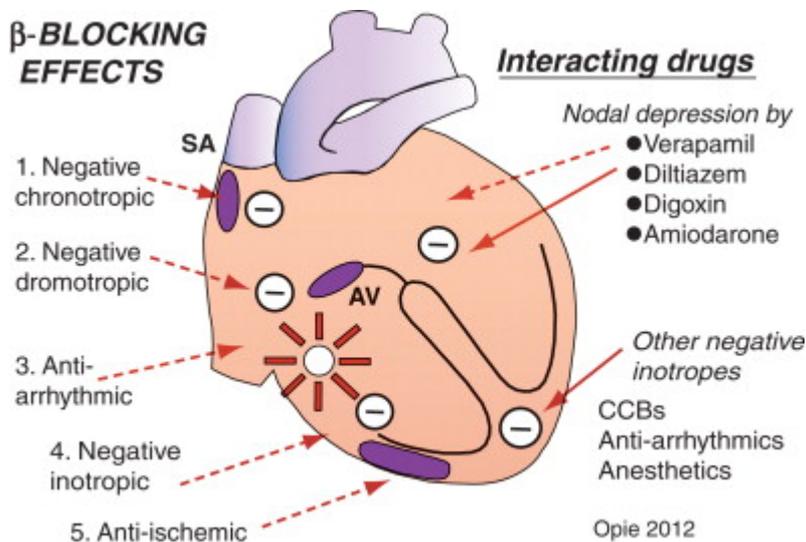
Figure 1-3 Cardiac effects of β-adrenergic blocking drugs at the levels of the sinoatrial (SA) node, atrioventricular (AV) node, conduction system, and myocardium. Major pharmacodynamic drug interactions are shown on the right.
(Figure © L. H. Opie, 2012.)
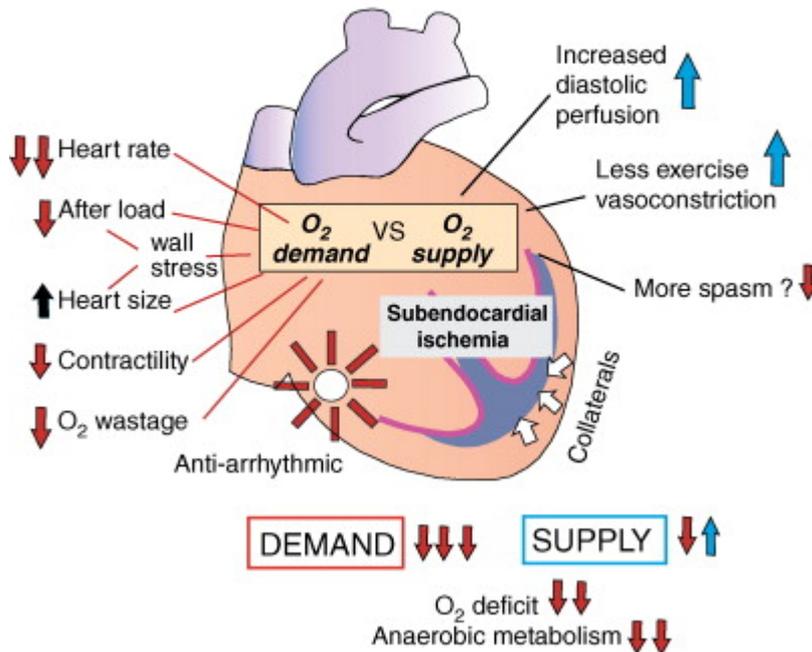
Figure 1-4 Effects of β-blockade on ischemic heart. β-blockade has a beneficial effect on the ischemic myocardium, unless there is vasospastic angina when spasm may be promoted in some patients. Note unexpected proposal that β-blockade diminishes exercise-induced vasoconstriction.
(Figure © L. H. Opie, 2012.)

Effects on coronary flow and myocardial perfusion.

Enhanced β-adrenergic stimulation, as in exercise, leads to β-mediated coronary vasodilation. The signaling system in vascular smooth muscle again involves the formation of cAMP, but, whereas the latter agent increases cytosolic calcium in the heart, it paradoxically decreases calcium levels in vascular muscle cells (see Fig. 3-2). Thus during exercise the heart pumps faster and more forcefully and the coronary flow is increased—a logical combination. Conversely, β-blockade should have a coronary vasoconstrictive effect with a rise in coronary vascular resistance. However, the longer diastolic filling time, resulting from the decreased heart rate in exercise, leads to better diastolic myocardial perfusion, to give an overall therapeutic benefit.

Effects on systemic circulation.

The effects previously described explain why β-blockers are antianginal as predicted by their developers. Antihypertensive effects are less well understood. In the absence of the peripheral dilatory actions of some β-blockers (see Fig. 1-11), it initially decrease the resting cardiac output by approximately 20% with a compensatory reflex rise in the peripheral vascular resistance. Thus within the first 24 hours of therapy, the arterial pressure is unchanged. The peripheral resistance then starts to fall after 1 to 2 days and the arterial pressure now starts to fall in response to decreased heart rate and cardiac output. Additional antihypertensive mechanisms may involve (1) inhibition of those β-receptors on the terminal neurons that facilitate the release of norepinephrine (prejunctional β-receptors), hence lessening adrenergic mediated vasoconstriction; (2) central nervous effects with reduction of adrenergic outflow; and (3) decreased activity of the renin-angiotensin system (RAS) because β-receptors mediate renin release (the latter mechanism may explain part of the benefit in heart failure).

Angina pectoris

Symptomatic reversible myocardial ischemia often reflects classical effort angina. Here the fundamental problem is inadequacy of coronary vasodilation in the face of increased myocardial oxygen demand, typically resulting from exercise-induced tachycardia (see Fig. 2-1). However, in many patients, there is also a variable element of associated coronary (and possibly systemic) vasoconstriction that may account for the precipitation of symptoms by cold exposure combined with exercise in patients with "mixed-pattern" angina. The choice of prophylactic antianginal agents should reflect the presumptive mechanisms of precipitation of ischemia.

β-blockade reduces the oxygen demand of the heart (see Fig. 1-4) by reducing the double product (heart rate × blood pressure [BP]) and by limiting exercise-induced increases in contractility. Of these, the most important and easiest to measure is the reduction in heart rate. In addition, an aspect frequently neglected is the increased oxygen demand resulting from left ventricular (LV) dilation, so that any accompanying ventricular failure needs active therapy.

All β-blockers are potentially equally effective in angina pectoris (see Table 1-1) and the choice of drug matters little in those who do not have concomitant diseases. *But a minority of patients do not respond to any β-blocker* because of (1) underlying severe obstructive coronary artery disease, responsible for angina even at low levels of exertion and at heart rates of 100 beats/min or lower; or (2) an abnormal increase in LV end-diastolic pressure resulting from an excess negative inotropic effect and a consequent decrease in subendocardial blood flow. Although it is conventional to adjust the dose of a β-blocker to secure a resting heart rate of 55 to 60 beats/min, in individual patients heart rates less than 50 beats/min may be acceptable provided that heart block is avoided and there are no symptoms. The reduced heart rate at rest reflects the relative increase in vagal tone as adrenergic stimulation decreases. A major benefit is the restricted increase in the *heart rate during exercise,* which ideally should not exceed 100 beats/min in patients with angina. The effectiveness of medical therapy for stable angina pectoris, in which the use of β-blockers is a central component, is similar to that of percutaneous coronary intervention with stenting.[10]

Combination antiischemic therapy of angina pectoris.

β-blockers are often combined with nitrate vasodilators and calcium channel blockers (CCBs) in the therapy of angina (see Table 2-4). However, the combined use of β-blockers with nondihydropyridine calcium antagonists (e.g., verapamil, diltiazem) should in general be avoided, because of the risks of excess bradycardia and precipitation of heart failure, whereas the combination with long-acting dihydropyridines is well documented.[11]

Co-therapy in angina.

Angina is basically a vascular disease that needs specific therapy designed to give long-term vascular protection. The following agents should be considered for every patient with angina: (1) aspirin and/or clopidogrel for antiplatelet protection, (2) statins and a lipid-lowering diet to decrease lipid-induced vascular damage, and (3) an ACE inhibitor that has proven protection from MI and with the doses tested (see Chapter 5, p. 143). Combinations of prophylactic antianginal agents are necessary in some patients to suppress symptoms, but have less clearcut prognostic implications.

Prinzmetal's variant angina.

β-blockade is commonly held to be ineffective and even harmful, because of lack of efficacy. On the other hand, there is excellent evidence for the benefit of CCB therapy, which is the standard treatment. In the case of *exercise-induced anginal attacks in patients with variant angina,* a small prospective randomized study in 20 patients showed that nifedipine was considerably more effective than propranolol.[12]

Cold intolerance and angina.

During exposure to severe cold, effort angina may occur more easily (the phenomenon of mixed pattern angina). Conventional β-blockade by propranolol is not as good as vasodilatory therapy by a CCB[13] and may reflect failure to protect from regional coronary vasoconstriction in such patients.[14]

Silent myocardial ischemia.

Episodes of myocardial ischemia, for example detected by continuous electrocardiographic recordings, may be precipitated by minor elevations of heart rate, probably explaining why β-blockers are very effective in reducing the frequency and number of episodes of silent ischemic attacks. In patients with silent ischemia and mild or no angina, atenolol given for 1 year lessened new events (angina aggravation, revascularization) and reduced combined end-points.[15]

β-blockade withdrawal.

Chronic β-blockade increases β-receptor density. When β-blockers are suddenly withdrawn, angina may be exacerbated, sometimes resulting in MI. Treatment of the withdrawal syndrome is by reintroduction of β-blockade. Best therapy is to avoid this condition by gradual withdrawal.

Acute coronary syndrome

Acute coronary syndrome (ACS) is an all-purpose term, including unstable angina and acute myocardial infarction (AMI), so that management is based on risk stratification (see Fig. 12-3). Plaque fissuring in the wall of the coronary artery with partial coronary thrombosis or platelet aggregation on an area of endothelial disruption is the basic pathologic condition. Urgent antithrombotic therapy with heparin (unfractionated or low molecular weight) or other antithrombotics, plus aspirin is the basic treatment (see Chapter 9). Currently, early multiple platelet–receptor blockade is standard in high-risk patients.

β-blockade is a part of conventional in-hospital quadruple therapy, the other three agents being statins, antiplatelet agents, and ACE inhibitors, a combination that reduces 6-month mortality by 90% compared with treatment by none of these.[16] β-blockade is usually started early, especially in patients with elevated BP and heart rate, to reduce the myocardial oxygen demand and to lessen ischemia (see Fig. 1-4). The major argument for early β-blockade is that threatened infarction, into which unstable angina merges, may be prevented from becoming overt.[17] Logically, the lower the heart rate, the less the risk of recurrent ischemia. However, the actual objective evidence favoring the use of β-blockers in unstable angina itself is limited to borderline results in one placebo-controlled trial,[18] plus only indirect evidence from two observational studies.[16],[19]

Acute ST-elevation myocardial infarction

Early ST-elevation myocardial infarction.

There are no good trial data on the early use of β-blockade in the reperfusion era. Logically, β-blockade should be of most use in the presence of ongoing pain,[20] inappropriate tachycardia, hypertension, or ventricular rhythm instability.[21] In the COMMIT trial early intravenous metoprolol given to more than 45,000 Asiatic patients, about half of whom were treated by lytic agents and without primary percutaneous coronary intervention, followed by oral dosing, led to 5 fewer reinfarctions and 5 fewer ventricular fibrillations per 1000 treated.[22] The cost was increased cardiogenic shock, heart failure, persistent hypotension and bradycardia (in total, 88 serious adverse events). In the United States, metoprolol and atenolol are the only β-blockers licensed for intravenous use in AMI. Overall, however, no convincing data emerge for routine early intravenous β-blockade.[23] With selected and carefully monitored exceptions, it is simpler to introduce oral β-blockade later when the hemodynamic situation has stabilized. The current American College of Cardiology (ACC)–American Heart Association (AHA) guidelines recommend starting half-dose oral β-blockade on day 2 (assuming hemodynamic stability) followed by dose increase to the full or the maximum tolerated dose, followed by long-term postinfarct β-blockade.[24]

Aha postinfarct recommendations 2011.

(1) Administer β-blockade for all postinfarct patients with an ejection fraction (EF) of 40% or less unless contraindicated, with use limited to carvedilol, metoprolol succinate, or bisoprolol, which reduce mortality *(Class 1, Level of Evidence A);* (2) administer β-blockade for 3 years in patients with normal LV function after AMI or ACS; *(Class 1, Level B).* It is also reasonable to continue β-blockade beyond 3 years *(Class IIa, Level B).*[25]

Benefits of postinfarct β-blockade.

In the postinfarct phase, β-blockade reduces mortality by 23% according to trial data[26] and by 35% to 40% in an observational study on a spectrum of patients including diabetics.[27] Timolol, propranolol, metoprolol, and atenolol are all effective and licensed for this purpose. Metoprolol has excellent long-term data.[28] Carvedilol is the only β-blocker studied in the reperfusion era and in a population also receiving ACE inhibitors.[29] As the LV dysfunction was an entry point, the carvedilol dose was gradually uptitrated, and all-cause mortality was reduced. The mechanisms concerned are multiple and include decreased ventricular arrhythmias[30] and decreased reinfarction.[31] β-Blockers with partial agonist activity are relatively ineffective, perhaps because of the higher heart rates.

The only outstanding questions are (1) whether low-risk patients really benefit from β-blockade (there is an increasing trend to omit β-blockade especially in patients with borderline hyperglycemic values); (2) when to start (this is flexible and, as data for early β-blockade are not strong,[26] oral β-blocker may be started when the patient's condition allows, for example from 3 days onward[29] or even later at about 1 to 3 weeks); and (3) how long β-blockade should be continued. Bearing in mind the risk of β-blockade withdrawal in patients with angina, many clinicians continue β-blockade administration for the long term once a seemingly successful result has been obtained. The benefit in high-risk groups such as older adults or those with low EFs increases progressively over 24 months.[27]

The *high-risk patients* who should benefit most are those often thought to have contraindications to β-blockade.[27] Although CHF was previously regarded as a contraindication to β-blockade, postinfarct patients with heart failure benefited more than others from β-blockade.[27] Today this category of patient would be given a β-blocker after treatment of fluid retention cautiously with gradually increasing doses of carvedilol, metoprolol, or bisoprolol. The SAVE trial[31] showed that ACE inhibitors and β-blockade are additive reducing postinfarct mortality, at least in patients with reduced EFs. The benefit of β-blockade when added to co-therapy by ACE inhibitors is a mortality reduction of 23% to 40%.[27],[29] Concurrent therapy by

CCBs or aspirin does not diminish the benefits of postinfarct β-blockade.

Despite all these strong arguments and numerous recommendations, β-blockers are *still underused in postinfarct patients* at the expense of many lives lost. In the long term, 42 patients have to be treated for 2 years to avoid one death, which compares favorably with other treatments.[26]

Lack of outcome studies in angina

Solid evidence for a decrease in mortality in postinfarct follow-up achieved by β-blockade has led to the assumption that this type of treatment must also improve the outcome in effort angina or unstable angina. Regretfully, there are no convincing outcome studies to support this proposal. In unstable angina, the short-term benefits of metoprolol were borderline.[18] In effort angina, a metaanalysis of 90 studies showed that β-blockers and CCBs had equal efficacy and safety, but that β-blockers were better tolerated[32] probably because of short-acting nifedipine capsules which were then often used. In angina plus hypertension, direct comparison has favored the CCB verapamil (see next section).

β-blockers for hypertension

β-blockers are no longer recommended as first-line treatment for hypertension by the Joint National Council (JNC) of the USA and have been relegated to fourth- or even fifth-line choices by the National Institute of Clinical Excellence of the UK.[33] β-blockers are the least effective of the standard antihypertensive drug classes at preventing major cardiovascular events, especially stroke.[34] β-blockers are more likely to predispose to new diabetes[35] and they are the least cost-effective of the major classes of antihypertensive agents (the costs of hospitalization, clinical events, and therapy of new diabetes).[36] The crucial study was ASCOT, in which the much better cardiovascular outcomes of amlodipine with or without perindopril compared with the atenolol with or without diuretic[34] could be explained by the lower central aortic pressures with amlopidine.[37] In 2003 JNC 7 listed the following as "compelling indications" for the use of β-blockers: heart failure with hypertension, post-MI hypertension, high coronary risk, and diabetes.[38] JNC 8 is due to appear this year and its view of β-blockers will elicit great interest. The exact mechanism of BP lowering by β-blockers remains an open question (see Fig. 7-10). A sustained fall of cardiac output and a late decrease in peripheral vascular resistance (after an initial rise) are important. Inhibition of renin release also contributes, especially to the late vasodilation. Of the large number of β-blockers now available, all are antihypertensive agents but few have outcome studies.[39]

| **Update: New Content Added** | *Date Added: 24 January 2013* |

Beta-blockers for hypertension
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Summary

Methods

The authors searched the Cochrane Central Register of Controlled Trials, Medline, Embase, and reference lists of previous reviews for eligible studies published since the previous Cochrane search in May 2006. The authors selected randomised controlled trials (RCTs) of at least one year duration, which assessed the effects of beta-blockers compared to placebo or other drugs, as first-line therapy for hypertension, on mortality and morbidity in adults.

Main results

The analysis included 13 RCTs which compared beta-blockers to placebo (4 trials, N=23,613), diuretics (5 trials, N=18,241), calcium-channel blockers (CCBs: 4 trials, N=44,825), and renin-angiotensin system(RAS) inhibitors (3 trials, N=10,828). Three-quarters of the 40,245 participants on beta-blockers used atenolol. Most studies had a high risk of bias, resulting from various limitations in study design, conduct, and data analysis.

Authors' conclusions

Initiating treatment of hypertension with beta-blockers leads to modest reductions in cardiovascular disease and no significant effects on mortality. These effects of beta-blockers are inferior to those of other antihypertensive drugs. The quality of this evidence

is low, implying that the true effect of beta-blockers may be substantially different from the estimate of effects found in this review. Further research should be of high quality and should explore whether

there are differences between different sub-types of beta-blockers or whether beta-blockers have differential effects on younger and elderly patients.

References

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For **patients at high risk of coronary artery disease,** such as those with diabetes, chronic renal disease, or a 10-year Framingham risk score of 10% or more, first-line antihypertensive choices should exclude β-blockers, according to the AHA.[40]

Hypertension plus effort angina: Risk of new diabetes.

In the INVEST study, in 6391 patients with hypertension and coronary artery disease followed for more than 2 years, the β-blocker atenolol gave similar major cardiovascular outcomes to the nondihydropyridine CCB verapamil, and yet the β-blocker group had more anginal episodes, new diabetes, and psychological depression.[41],[42] More new diabetes in the atenolol group could be explained by (1) the greater use of add-on diuretics and (2) the greater use of an ACE inhibitor, trandolapril, in the verapamil group.

Older adult patients.

In certain hypertension subgroups such as older adults, especially those with left ventricular hypertrophy (LVH), comparative studies show better outcome data with the other agents such as diuretics[43] and the angiotensin receptor blocker (ARB) losartan.[44] One possible reason is that at equivalent brachial artery pressures, β-blockade reduces the central aortic pressure less than other agents.[45]

Black patients.

In black older adults, atenolol was only marginally more antihypertensive than placebo.[46] Unexpectedly, in younger blacks (age less than 60 years), atenolol was the second most effective agent, following diltiazem, and more effective than the diuretic hydrochlorothiazide.[46]

Diabetic hypertensives.

BP-reducing therapy based on atenolol versus captopril showed no major differences nor even trends, although the β-blocker group had gained weight and more often needed additional glucose-lowering treatment to control the blood sugar.[47]

Combination antihypertensive therapy.

To reduce the BP, β-blockers may be combined with CCBs, α-blockers, centrally active agents, and cautiously with diuretics. Because β-blockers reduce renin levels, combination with ACE inhibitors or an ARB is not so logical. Increased new diabetes is a risk during β-blocker-thiazide cotherapy.[35],[48] Much less well tested is the use of carvedilol that may increase insulin sensitivity.[49] *Ziac* is bisoprolol (2.5 to 10 mg) with a very low dose of hydrochlorothiazide (6.25 mg). This drug combination has been approved as first-line therapy (starting with bisoprolol 2.5 mg plus thiazide 6.25 mg) for systemic hypertension by the Food and Drug Administration, an approval rarely given to a combination product. Metabolic side effects of higher thiazide doses were minimized and there was only a small increase in fatigue and dizziness. In the United States, atenolol and chlorthalidone (Tenoretic) and metoprolol tartrate and hydrochlorothiazide (Lopressor HCT) are combinations widely used, yet they often contain diuretic doses that are higher than desirable (e.g., chlorthalidone 25 mg; see Chapter 7). Combinations of such prodiabetic doses of diuretics with β-blockade, in itself a risk for new diabetes,[50] is clearly undesirable. Note that standard doses of β-blocker or diuretic even separately predispose to new diabetes.[35] In the ASCOT hypertension study, amlodipine with or without perindopril gave better outcomes than atenolol with or without bendroflumethiazide, including less new diabetes (see Chapter 7).

β-blockers for arrhythmias

β-blockers have multiple antiarrhythmic mechanisms (Fig. 1-5) and are effective against many supraventricular and ventricular arrhythmias. Basic studies show that they counter the arrhythmogenic effects of excess catecholamine stimulation by countering the proarrhythmic effects of increased cAMP and calcium-dependent triggered arrhythmias.[51],[52] Logically, β-blockers should be particularly effective in arrhythmias caused by increased adrenergic drive (early phase AMI, heart failure, pheochromocytoma, anxiety, anesthesia, postoperative states, and some exercise-related arrhythmias, as well as mitral valve prolapse) or by increased cardiac sensitivity to catecholamines (thyrotoxicosis). β-blockade may help in the prophylaxis of SVTs by inhibiting the initiating atrial ectopic beats and in the treatment of SVT by slowing the AV node and lessening the ventricular response rate. Perhaps surprisingly, in sustained ventricular tachyarrhythmias the empirical use of metoprolol was as effective as electrophysiologically guided antiarrhythmic therapy.[53] Likewise, in ventricular tachyarrhythmias, the ESVEM study showed that sotalol, a β-blocker with added Class III activity (Fig. 1-5), was more effective than a variety of Class I antiarrhythmics.[54]
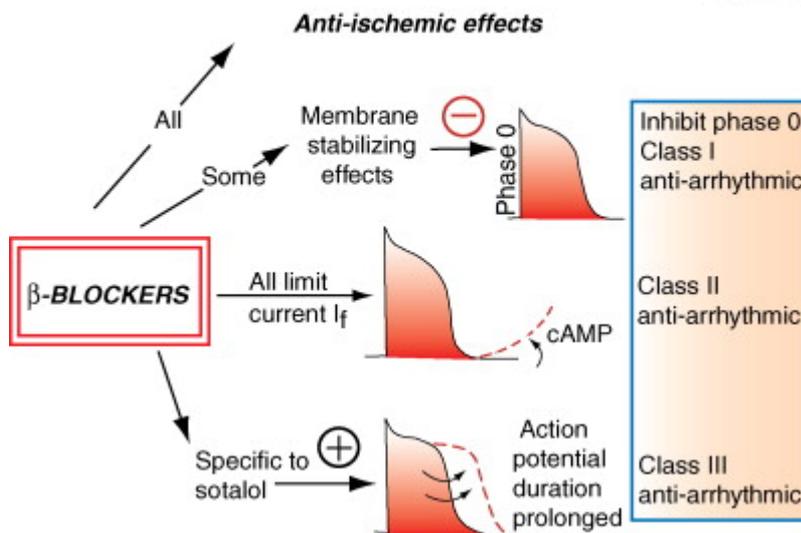
Figure 1-5 Antiarrhythmic properties of β-blockers. Antiischemic effects indirectly lessen arrhythmias. Note that only sotalol has added Class-III antiarrhythmic effects. It is questionable whether the membrane stabilizing effects of propranolol confer additional antiarrhythmic properties.
(Figure © L. H. Opie, 2012.)

In patients with atrial fibrillation, current management practices often aim at control of ventricular rate ("rate control") rather than restoration and maintenance of sinus rhythm ("rhythm control"). β-blockers, together with low-dose digoxin, play an important role in rate control in such patients.

In postinfarct patients, β-blockers outperformed other antiarrhythmics[26] and decreased arrhythmic cardiac deaths.[55] In postinfarct patients with depressed LV function and ventricular arrhythmias, a retrospective analysis of data from the CAST study shows that β-blockade reduced all-cause mortality and arrhythmia deaths.[56] Although the mechanism of benefit extends beyond antiarrhythmic protection,[57] it is very unlikely that β-blockers can match the striking results obtained with an implantable defibrillator (23%

mortality reduction in Class 2-3 heart failure).[57],[58] In *perioperative patients,* β-blockade protects from atrial fibrillation.[59]

Intravenous esmolol is an ultrashort-acting agent esmolol that has challenged the previously standard use of verapamil or diltiazem in the perioperative period in acute SVT, although in the apparently healthy person with SVT, adenosine is still preferred (see Chapter 8). Intravenous esmolol may also be used acutely in atrial fibrillation or flutter to reduce the rapid ventricular response rate (see later).

β-blockers in heart failure

That β-blockers, with their negative inotropic effects, could increase cardiac contraction and decrease mortality in heart failure is certainly counterintuitive, especially bearing in mind that the β_1-receptor is downregulated (Fig. 1-6). Not only does the cardiac output increase, but abnormal patterns of gene expression revert toward normal.[60] Several mechanisms are proposed, of which the first three are well-studied.

1. *Improved β-adrenergic signaling*. Myocardial β-receptors respond to prolonged and excess β-adrenergic stimulation by internalization and downregulation (see Fig. 1-6), so that the β-adrenergic inotropic response is diminished. This is a self-protective mechanism against the known adverse effects of excess adrenergic stimulation. The first step in β_1-receptor internalization is the increased activity of β_1ARK, now renamed GRK_2. GRK_2 then phosphorylates the β_1-receptor, which in the presence of β-arrestin becomes uncoupled from G_s and internalizes (Fig. 1-7).[4] If the β-stimulation is sustained, then the internalized receptors may undergo lysosomal destruction with true loss of receptor density or downregulation. However, *downregulation* is a term also often loosely applied to any step leading to loss of receptor response. Experimental β-blockade decreases the expression of GRK_2 and increases the activity of AC, thereby improving contractile function. *Relative upregulation of the β2-receptor may have* inhibitory effects (see Fig. 1-6), including continued excessive formation of G_i and hyperphosphorylated SR (see Fig. 1-7). However, the role of the β_2-receptor in advanced heart failure is still not fully clarified.[8] Thus not surprisingly in clinical heart failure studies carvedilol with its blockade of β_1, β_2, and β_3 receptors is superior to the β_1-selective blocker metoprolol.[61],[62]

2. *Self-regulation.* There is a potent and rapid physiologic switch-off feedback mechanism that mutes β-adrenergic receptor stimulation and avoids perpetuated activation of this receptor (see Fig. 1-7). Physiologically, this very rapid *desensitization of the β-receptor* occurs within minutes to seconds. Sustained β-agonist stimulation rapidly induces the activity of the GRK_2, thereby increasing the affinity of the β-receptor for another protein family, the *arrestins* that dissociate the agonist-receptor complex. β-arrestin not only lessens the activation of AC, thereby inhibiting is activity,[63] but furthermore switches the agonist coupling from G_s to inhibitory G_i.[64]

EXCESS β-ADRENERGIC SIGNALS IN HF

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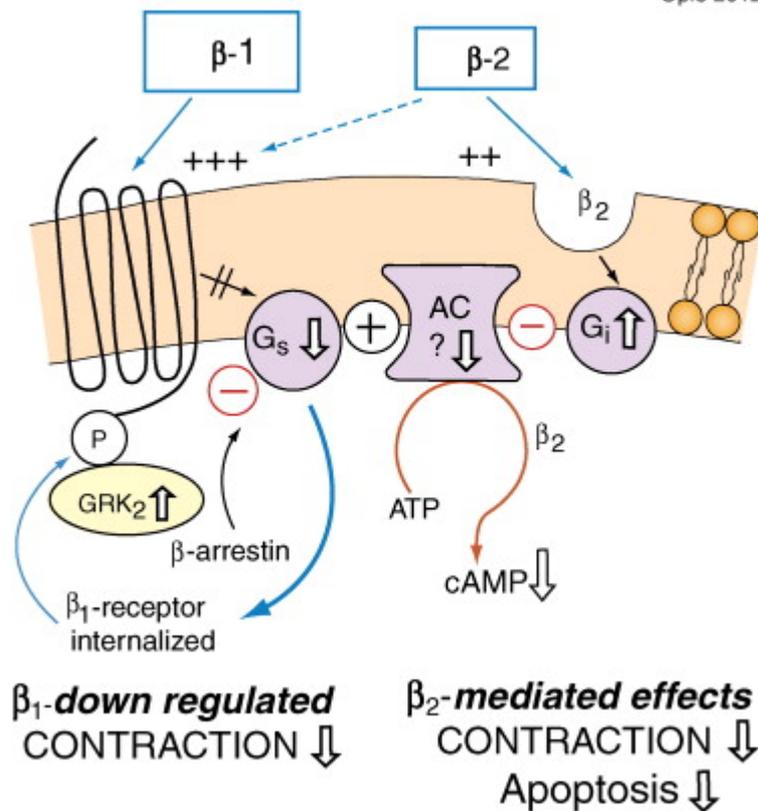
Figure 1-6 β-adrenergic receptors in advanced heart failure. Downregulation and uncoupling of β-adrenergic receptor signal systems results in depressed levels of cyclic adenosine monophosphate (cAMP) and decreased contractility, which may be viewed as an autoprotective from the adverse effects of cAMP. Note: (1) β-receptor downregulation starts as a result of inhibitory phosphorylation of the receptor mediated by G protein–coupled receptor kinase (GRK2;previously β1 adrenergic receptor kinase [β1ARK]), GRK2 increases in response to excess β-adrenergic stimulation of the receptor, (2) β-receptor uncoupling from Gs results from β-arrestin activity, (3) β-receptor downregulation is a result of internalization, (4) increased GI is a result of increased messenger ribonucleic acid activity, (5) β2 receptors are relatively upregulated and appear to exert an inhibitory effect on contractile via enhanced GI.
(For details see Opie LH, Heart Physiology from Cell to Circulation. Lippincott Williams and Wilkins, Philadelphia, 2004:508.) (Figure © L. H. Opie, 2012.)
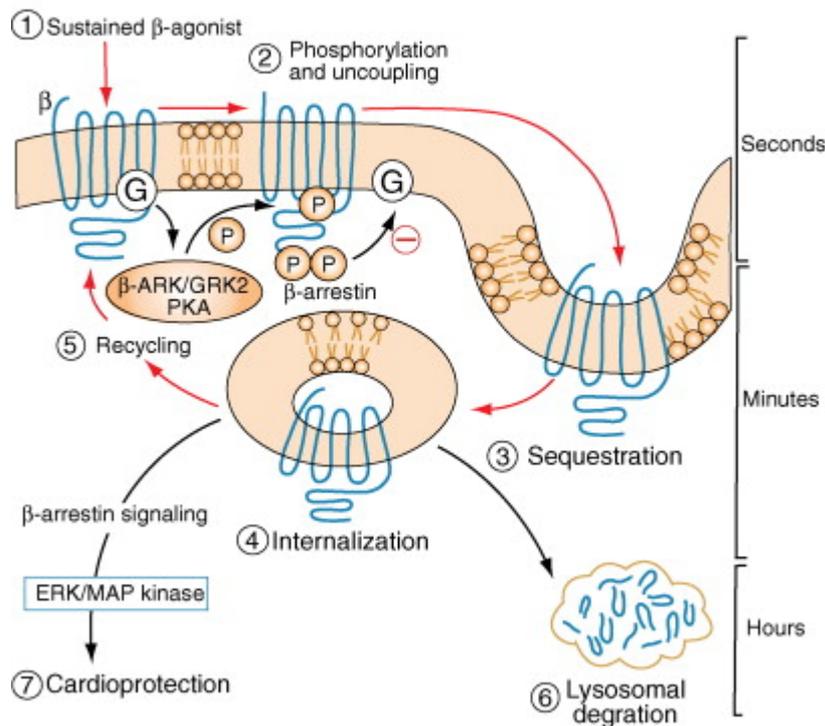
Figure 1-7 Mechanisms of β-adrenergic receptor desensitization and internalization. Note the internalized receptor complex with growth stimulation via mitogen-activated protein (MAP) kinase. *β-ARK*, β-agonist receptor kinase; *ERK,* extracellular signal-regulated kinase; *GRK2*, G protein–coupled receptor kinase; *PKA,* protein kinase A.
(Adapted from Hein L, Kobilka BK: Adrenergic receptors. From molecular structures in vivo function. Trends Cardiovasc Med 1997;7:137.) (Figure © L. H. Opie, 2012.)

Resensitization of the receptor occurs if the phosphate group is split off by a phosphatase so that the receptor may then more readily be linked to G_s. β-arrestin signaling can also evoke an alternative counterbalancing protective path by activating the epidermal growth factor receptor that leads to the protective ERK/MAP kinase path (see item 7 in Fig. 1-7).[65] β-blocker drugs may have complex effects by β-arrestin agonism.[66] Although receptor-arrestin effects are best described for the β2-receptor, they also occur to a lesser extent with the β1-receptor.[63]

In heart failure, prolonged hyperadrenergic β-receptor stimulation is linked to adverse end results, both impairing contractile function and enhancing adverse signaling. There is long-term compensatory desensitization of the β-adrenergic receptor in chronic heart failure.[67] Conversely, transgenic mice with GRK2 (previously Beta-adrenergic receptor kinase, BARK) overexpression are protected from heart failure.[67] Of note, the desensitization process is reversible as occurs during experimental cardiac resynchronization therapy, when specific suppressors of the inhibitor G protein (see G_i in Fig. 1-6) are much increased in activity so that β-adrenergic signaling becomes more normal.[68]

3. *The hyperphosphorylation hypothesis.* The proposal is that continued excess adrenergic stimulation leads to hyperphosphorylation of the calcium-release channels (also known as the *ryanodine receptor*) on the SR. This causes defective functioning of these channels with excess calcium leak from the SR, with cytosolic calcium overload. Because the calcium pump that regulates calcium uptake into the SR is simultaneously downregulated, the pattern of rise and fall of calcium ions in the cytosol is impaired with poor contraction and delayed relaxation. These abnormalities are reverted toward normal with β-blockade,[69],[70] which also normalizes the function of the calcium release channel.[71]

Update: New Content Added

Date Added: 07 February 2013

Beta-2 Adrenergic signaling links upregulation of G protein-coupled receptor kinase 2 to heart failure

Lionel H. Opie, MD, DPhil, Professor of Medicine Em., Hatter Insitute for Cardiovascular Research in Africa, University of Cape Town Medical School, and Groote Schuur Hospital, Observatory, Cape Town, South Africa

Summary

Background. Can lifestyle intervention achieve remission in type 2 diabetes?

Background:. Upregulation of G protein-coupled receptor kinase 2 (GRK2) is a well-established causal factor of heart failure, but the underlying mechanism is poorly understood. See Figs. 1-6 and 1-7 in this book.

Methods and Results: The authors state as follows:" Overexpression of GRK2 led to a G(i)-dependent decrease of contractile response to βAR stimulation in cultured mouse cardiomyocytes and in vivo. Importantly, cardiac-specific transgenic overexpression of a mutant β(2)AR lacking PKA phosphorylation sites (PKA-TG) but not the wild-type β(2)AR (WT-TG) or a mutant β(2)AR lacking GRK sites (GRK-TG) led to exaggerated cardiac response to pressure overload, as manifested by markedly exacerbated cardiac maladaptive remodeling and failure and early mortality. Furthermore, inhibition of G(i) signaling with pertussis toxin restores cardiac function in heart failure associated with increased β(2)AR to G(i) coupling induced by removing PKA phosphorylation of the receptor and in GRK2 transgenic mice, indicating that enhanced phosphorylation of β(2)AR by GRK and resultant increase in G(i)-biased β(2)AR signaling play an important role in the development of heart failure."

Comment:

This is an important paper to clarify the contradictory effects of beta-stimulation, both physiologically increasing the inotropic state while playing a role in the development of heart failure For the clinician, this study gives mechanistic support for the use of combined alpha-beta blockers such as carvedilol in the therapy of heart failure…

The authors summarize as follows: "Our data show that enhanced β(2)AR phosphorylation by GRK, in addition to PKA, leads the receptor to G(i)-biased signaling, which, in turn, contributes to the pathogenesis of heart failure, marking G(i)-biased β(2)AR signaling as a primary event linking upregulation of GRK to cardiac maladaptive remodeling, failure and cardiodepression."

References

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4. *Bradycardia.* β-blockade may act at least in part by reduction of the heart rate (Fig. 1-8). Multiple studies have suggested that a high resting heart rate is an independent risk factor for cardiovascular disease,[72] which could reflect the role of excess adrenergic tone. Bradycardia may improve coronary blood flow and decrease the myocardial oxygen demand. Experimentally, long-term heart rate reduction lessens extracellular matrix collagen, besides improving the LV EF.[73] To achieve adequate bradycardia, the addition of ivabradine may be required (see Chapter 6, p. 195).

5. *Protection from catecholamine myocyte toxicity.* The circulating concentrations of norepinephrine found in severe heart failure are high enough to be directly toxic to the myocardium, experimentally damaging the membranes and promoting subcellular destruction, acting at least in part through cytosolic calcium overload.[74]

6. *Antiarrhythmic effects.* In experimental heart failure, ventricular arrhythmias are promoted via increased formation of cAMP and calcium-mediated afterpotentials.[52]
7. *Antiapoptosis.* Coupling of the β_2-receptor to the inhibitory G-protein, G_1, may be antiapoptotic.[75]
8. *Renin-angiotensin inhibition.* When added to prior ACE inhibitor or ARB therapy, β-blockade by metoprolol increases the blockade of the RAS.[62]

β-BLOCKADE IN HEART FAILURE

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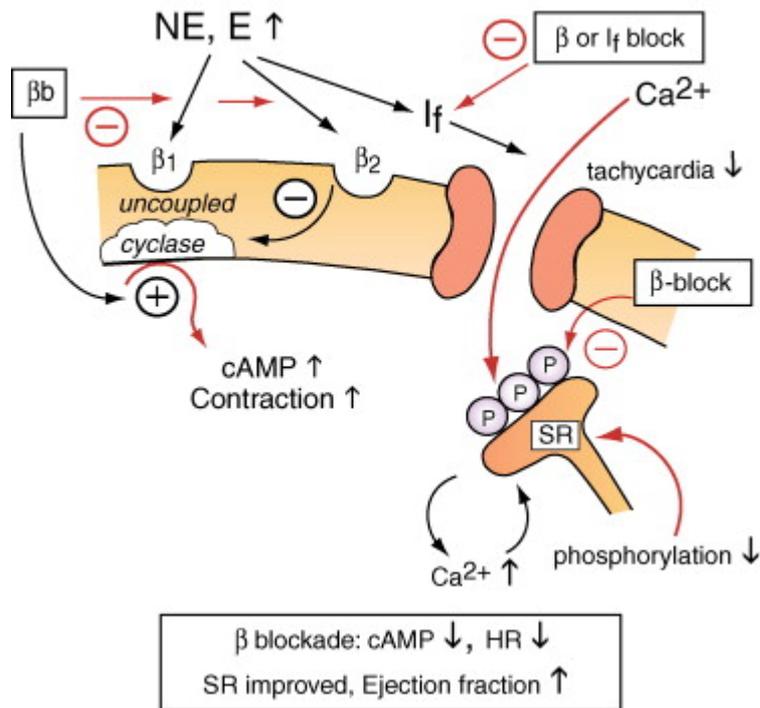
Figure 1-8 Proposed mechanisms of action of β-blockade in heart failure. By inhibiting the effects of norepinephrine (NE) and epinephrine (E), β-blockade lessens the feedback mechanism whereby G protein–receptor kinase inhibits receptor activity (see Fig. 1-6). β-blockade therefore indirectly increases formation of cyclic adenosine monophosphate (cAMP) and improves contractions. β-blockade, by reducing the heart rate, lessens calcium entry into failing myocytes to decrease cytosolic calcium overload. This bradycardia is achieved by inhibition of the current If and other nonspecific pacemaking currents. Thirdly, β-blockade inhibits the phosphorylation of the sarcoplasmic reticulum (SR) and therefore facilitates calcium ion release and, indirectly, uptake of calcium by the SR (see Fig. 1-7).
(Figure © L. H. Opie, 2012.)

How to apply β-blockers in heart failure

β-blockers are now recognized as an integral part of anti–heart failure therapy based on neurohumoral antagonism[76] with coherent molecular mechanisms (see Fig. 1-8).[76] They benefit a wide range of patients with stable systolic heart failure, including women, diabetics, older adults as in the nebivolol study (SENIORS), and, in several studies, black patients.[77] The principles are the following: (1) Select patients with stable heart failure; start slowly and uptitrate gradually (Table 1-2),[78] while watching for adverse effects. If necessary cut back on the dose or titrate more slowly. (2) The usual procedure is to add β-blockade to existing therapy, including ACE inhibition and diuretics, and, optionally in some studies, digoxin, when the patient is hemodynamically stable and not in Class IV or severe Class III failure. (3) However, in several recent studies,[79],[80] β-blockers were also given before ACE inhibitors, which is logical, considering that excess baroreflex-mediated adrenergic activation may be an important initial event in heart failure (see Fig. 5-8). (4) Never stop the β-blocker abruptly (risk of ischemia and infarction). (5) Use only β-blockers with doses that are well understood and clearly delineated, and with proven benefit, notably carvedilol, metoprolol, bisoprolol, and nebivolol (see Table 1-2). The first three of these drugs have *reduced mortality* in large trials by approximately one third. Of these, only carvedilol and long-acting metoprolol are

approved in the United States. However, data for carvedilol are strongest in the COMET trial[61]; carvedilol reduced mortality more than metoprolol. Thus far there is no evidence that diastolic heart failure improves.[78]

Table 1-2   -- Heart Failure: A Firm Indication for β-Blockade—Titration and Doses of Drugs*

β-Blocker	First Dose	Third Week	Fifth-Sixth Week	Final Dose
Carvedilol	3.125	6.25 × 2	12.5 × 2	25 × 2
Metoprolol SR	25[†]	50	100	200
Bisoprolol	1.25	3.75	5	10
Nebivolol	1.25	2.5	5	10

*All doses in milligrams. Data from placebo-controlled large trials, adapted from McMurray, Heart, 1999, 82 (suppl IV), 14-22. For exact nebivolol dosage in older adults, here modified, see reference 78. Forced titration in all studies, assuming preceding dose tolerated. Dose once daily for metoprolol and bisoprolol and twice daily for carvedilol. Carvedilol doses from US package insert. Doses taken with food to slow absorption; target dose may be increased to 50 mg bid for patients > 85 kg.

†Slow-release metoprolol (CR/XL formulation), reduce initial dose to 12.5 mg in severe heart failure.

For every heart rate reduction of 5 beats/min with β-blockade, there is an 18% reduction (cardiac index, 6%-29%) in the risk for death as occurred in the 23 β-blocker trials in 19,209 patients, of whom more than 95% had systolic dysfunction.[81] Perhaps unexpectedly, the dose of β-blocker did not relate to any benefit. The initiation of β-blockade is a slow process that requires careful supervision and may temporarily worsen the heart failure; we strongly advise that only the proven β-blockers be used in the exact dose regimens that have been tested (see Table 1-2). Propranolol, the original gold-standard β-blocker, and atenolol, two commonly used agents, have not been well studied in heart failure.

Other cardiac indications

In *hypertrophic obstructive cardiomyopathy,* high-dose propranolol is standard therapy although verapamil and disopyramide are effective alternatives.

In *catecholaminergic polymorphic ventricular tachycardia* high-dose β-blockers prevent exercise-induced ventricular tachycardia (VT), although most patients continue to have ventricular ectopy during exercise, so that heart rate–reducing calcium blockers may give added benefit.[82]

In *mitral stenosis with sinus rhythm,* β-blockade benefits by decreasing resting and exercise heart rates, thereby allowing longer diastolic filling and improved exercise tolerance. In mitral stenosis with chronic atrial fibrillation, β-blockade may have to be added to digoxin to obtain sufficient ventricular slowing during exercise. Occasionally β-blockers, verapamil, and digoxin are all combined. Heart block is a risk during co-therapy of β-blockers with verapamil.

In mitral valve prolapse, β-blockade is the standard procedure for control of associated arrhythmias.

In dissecting aneurysms, in the hyperacute phase, intravenous propranolol has been standard, although it could be replaced by esmolol. Thereafter, oral β-blockade is continued.

In Marfan syndrome with aortic root involvement, β-blockade is likewise used against aortic dilation and possible dissection.

In neurocardiogenic (vasovagal) syncope, β-blockade should help to control the episodic adrenergic reflex discharge believed to contribute to symptoms. However, a detailed study on 208 patients showed that metoprolol did not work.[83]

In Fallot's tetralogy, propranolol 2 mg/kg twice daily is usually effective against the cyanotic spells, probably acting by inhibition of right ventricular contractility.

Congenital QT-prolongation syndromes are now classified both on the basis of genotype and phenotype. β-blocker therapy is theoretically most effective when the underlying mutation affects K^+ channel–modulated outward currents. β-blockers reduce the overall frequency of major and minor cardiac events by approximately 60%, thus not eliminating the need for implantable defibrillator insertion in high-risk patients.[84] In the related condition of *catecholaminergic polymorphic VT,* β-blockers are also moderately effective.[85]

In postural tachycardia syndrome (POTS), both low-dose propranolol (20 mg)[86] and exercise training are better than high-dose propranolol (80 mg daily).[87]

Update: New Content Added	*Date Added: 14 February 2013*

Inappropriate sinus tachycardia: ivabradine as an alternative to beta-blockade

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Summary

Background: The purpose of this study was to investigate the role of ivabradine, the blocker of the If pacemaker current, in the treatment the high discharge rate from sinus node cells that causes symptomatic inappropriate sinus tachycardia (1).

Methods: Twenty-one patients were randomized to receive placebo (n = 10) or ivabradine 5 mg twice daily (n = 11) for 6 weeks. After a washout period, patients crossed over for an additional 6 weeks. Each patient underwent symptom evaluation and heart rate assessment at the start and finish of each phase.

Results: After taking ivabradine, patients reported that >70% of symptoms were eliminated (relative risk: 0.25; 95% CI: 0.18 to 0.34; p < 0.001), with 47% of them experiencing complete elimination. Heart rate at rest fell from 88 ± 11 beats/min to 76 ± 11 beats/min, p = 0.011). Standing heart rate fell from 108 ± 12 beats/min to 92 ± 11 beats/min, p < 0.0001). 24 h heart rate fell from 88 ± 5 beats/min to 77 ± 9 beats/min, p = 0.001). Effort heart rate fell from 176 ± 17 beats/min to 158 ± 16 beats/min, p = 0.001. No cardiovascular side effects were encountered

Ivabradine vs, beta-blockade. A comparative study enrolled enrolled 20 patients resistant to previous therapy by beta-blockers or verapamil (2) . After 4 weeks of treatment with metoprolol succinate (up to 190 mg once a day) the therapy was switched to ivabradine up to 7.5 mg twice daily. Resting heart rate fell both for metoprolol and for ivabradine compared with baseline. During daily activity there was an even larger decrease of heart rate on ivabradine than on metoprolol, and both were significantly different from untreated heart rates.. Ivabradine was very well tolerated whereas some patients on metoprolol developed hypotension or bradycardia requiring dose reduction. Significantly lower incidence of symptoms were found on ivabradine therapy than on metoprolol. Although both metoprolol and ivabradine reduced heart rate,ivabradine seemed to be more effective in relieving symptoms.

Conclusions: Both of these small studies shows that in symptomatic patients with inappropriate sinus tachycardia, symptoms may improve when given ivabradine which blocks the If pacemaker current. In the one study (1), there had been no prior beta-blockade. The principle of blockade of the If pacemaker current for symptomatic improvement of this rather unusual condition is likely to hold. Beta-blockade also blocks this pacemaking current and was effective in the other small study (2). In countries such as the USA where ivabradine is not (yet) registered for use, beta-blockade remains the therapy of first choice. Cleary larger, more definitive long term trials are required to further clarify which therapy is better.

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Noncardiac indications for β-blockade

Stroke.

In an early trial the nonselective blocker propranolol was only modestly beneficial in reducing stroke (although ineffective in reducing coronary artery disease [CAD]).[88] The β_1 selective agents are more effective in stroke reduction.[89]

Vascular and noncardiac surgery.

β-blockade exerts an important protective effect in selected patients. Perioperative death from cardiac causes and MI were reduced by bisoprolol in high-risk patients undergoing vascular surgery.[90] A risk-based approach to noncardiac surgery is proposed by a very large observational study on 782,969 patients. In those at no or very low cardiac risk, β-blockers were without benefit and in fact were associated with more adverse events, including mortality. In those at very high cardiac risk, mortality decreased by 42%, with a number needed to treat of only 33.[91] Thus risk factor assessment is vital (see original article for revised cardiac risk index). In patients undergoing vascular surgery, but otherwise not at very high risk, perioperative metoprolol gave no benefit yet increased intraoperative bradycardia and hypotension.[92]

Impact of poise study.

In the major prospective POISE (PeriOperative ISchemic Evaluation) study on a total of 8,351 patients, perioperative slow-release metoprolol decreased the incidence of nonfatal MI from 5.1% to 3.6% (p < 0.001), yet increased total perioperative mortality from 2.3% to 3.1% (p < 0.05), with increased stroke rates and markedly increased significant hypotension and bradycardia. *Thus routine perioperative inception of metoprolol therapy is not justified.* As metoprolol exerts markedly heterogenous cardiovascular effects according to metabolic genotype, involving subtypes of cytochrome P450 2D6,[93] genetic differences may have accounted for part of the adverse cardiovascular findings in POISE and another study.[92]

In an important focused update given by ACC-AHA,[94] the major recommendations are the following: (1) Class I indication for perioperative β-blocker use in patients already taking the drug; (2) Class IIa recommendations for patients with inducible ischemia, coronary artery disease, or multiple clinical risk factors who are undergoing vascular (i.e., high-risk) surgery and for patients with coronary artery disease or multiple clinical risk factors who are undergoing intermediate-risk surgery; (3) Initiation of therapy, particularly in lower-risk groups, requires careful consideration of the risk/benefit ratio; (4) If initiation is selected, it should be started well before the planned procedure with careful perioperative titration to achieve adequate heart rate control while avoiding frank bradycardia or hypotension. In the light of the POISE results, routine administration of perioperative β-blockers, particularly in higher fixed-dose regimens begun on the day of surgery, cannot be advocated.

Thyrotoxicosis.

Together with antithyroid drugs or radioiodine, or as the sole agent before surgery, β-blockade is commonly used in thyrotoxicosis to control symptoms, although the hypermetabolic state is not decreased. β-blockade controls tachycardia, palpitations, tremor, and nervousness and reduces the vascularity of the thyroid gland, thereby facilitating operation. In thyroid storm, intravenous propranolol can be given at a rate of 1 mg/min (to a total of 5 mg at a time); circulatory collapse is a risk, so that β-blockade should only be used in thyroid storm if LV function is normal as shown by conventional noninvasive tests.

Anxiety states.

Although propranolol is most widely used in anxiety (and is licensed for this purpose in several countries, including the United States), probably all β-blockers are effective, acting not centrally but by a reduction of

peripheral manifestations of anxiety such as tremor and tachycardia.

Glaucoma.

The use of local β-blocker eye solutions is now established for open-angle glaucoma; care needs to be exerted with occasional systemic side effects such as sexual dysfunction, bronchospasm, and cardiac depression. Among the agents approved for treatment of glaucoma in the United States are the nonselective agents timolol (Timoptic), carteolol, levobunolol, and metipranolol. The cardioselective betaxolol may be an advantage in avoiding side effects in patients with bronchospasm.

Migraine.

Propranolol (80 to 240 mg daily, licensed in the United States) acts prophylactically to reduce the incidence of migraine attacks in 60% of patients. The mechanism is presumably by beneficial vasoconstriction. The antimigraine effect is prophylactic and not for attacks once they have occurred. If there is no benefit within 4 to 6 weeks, the drug should be discontinued.

Esophageal varices.

β-blockade has been thought to prevent bleeding by reducing portal pressure. No benefit was found in a randomized study.[95]

Pharmacologic properties of various β-blockers

β-blocker "generations."

First-generation nonselective agents, such as propranolol, block all the β-receptors (both β_1 and β_2). *Second-generation cardioselective agents,* such as atenolol, metoprolol, acebutolol, bisoprolol, and others, have, when given in low doses, relative selectivity for the β_1 (largely cardiac) receptors (Fig. 1-9). *Third-generation vasodilatory* agents have added properties (Fig. 1-10), acting chiefly through two mechanisms: first, direct vasodilation, possibly mediated by release of nitric oxide as for carvedilol (see Fig. 1-10) and nebivolol,[6] and, second, added α-adrenergic blockade, as in labetalol and carvedilol. A third vasodilatory mechanism, as in pindolol and acebutolol, acts via β_2-intrinsic sympathomimetic activity (ISA), which stimulates arterioles to relax; however, these agents are less used at present and do not neatly fit into the division of the three "generations." Acebutolol is a cardioselective agent with less ISA than pindolol that was very well tolerated in a 4-year antihypertensive study.[96]
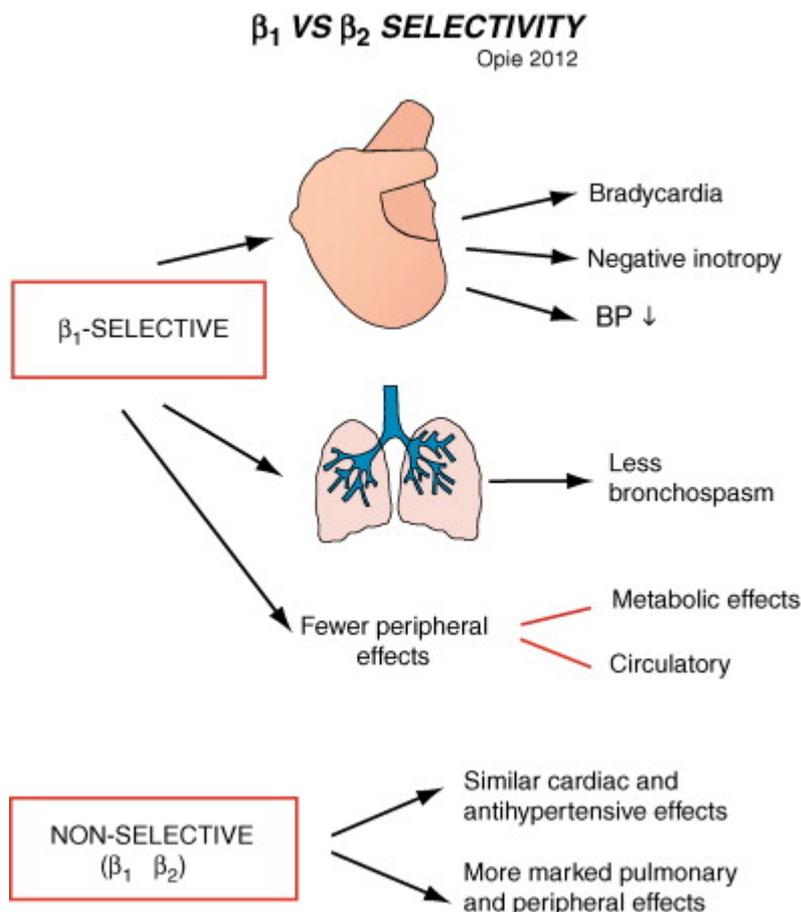
Figure 1-9 β_1- versus β_2-cardioselectivity. In general, note several advantages of cardioselective β-blockers (exception: heart failure). Cardioselectivity is greatest at low drug doses.
(Figure © L. H. Opie, 2012.)

VASODILATORY β-BLOCKERS

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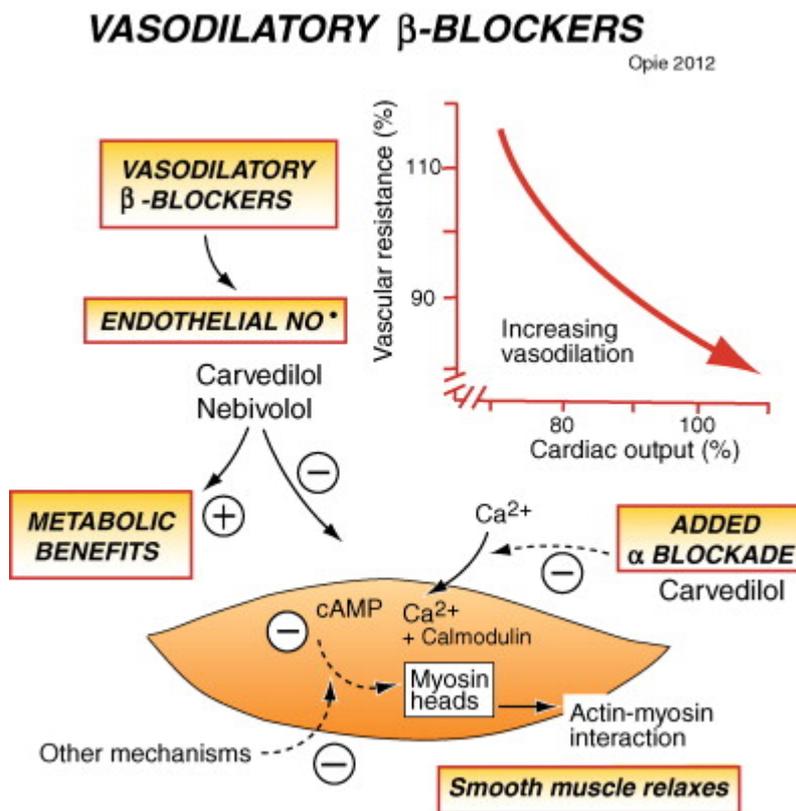
Figure 1-10 Vasodilatory mechanisms and effects. Vasodilatory β-blockers tend to decrease the cardiac output less as the systemic vascular resistance falls. Vasodilatory mechanisms include α-blockade (carvedilol), formation of nitric oxide (nebivolol and carvedilol), and intrinsic sympathomimetic activity (ISA). ISA, as in pindolol, has a specific effect in increasing sympathetic tone when it is low, as at night, and increasing nocturnal heart rate, which might be disadvantageous in nocturnal angina or unstable angina.
(Figure © L. H. Opie, 2012.)

Nonselective agents (combined β$_1$-β$_2$-blockers).

The prototype β-blocker is propranolol, which is still often used worldwide and is a World Health Organization essential drug. By blocking β$_1$-receptors, it affects heart rate, conduction, and contractility, yet by blocking β$_2$-receptors, it tends to cause smooth muscle contraction with risk of bronchospasm in predisposed individuals. This same quality might, however, explain the benefit in migraine when vasoconstriction could inhibit the attack. Among the nonselective blockers, nadolol and sotalol are much longer acting and lipid-insoluble.

Combined β$_1$–β$_2$–α-blocker.

Carvedilol is very well supported for preferential use in heart failure, in which this combination of receptor blockade should theoretically be ideal, as shown by better outcomes than with metoprolol in the COMET study.[97]

Cardioselective agents (β$_1$-selectivity).

Cardioselective agents (acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, and metoprolol) are as antihypertensive as the nonselective ones (see Fig. 1-9). Selective agents are preferable in patients with chronic lung disease or chronic smoking, insulin-requiring diabetes mellitus, and in stroke prevention.[89] Cardioselectivity varies between agents, but is always greater at lower doses. Bisoprolol is among the most selective. Cardioselectivity declines or is lost at high doses. No β-blocker is completely safe in the presence of asthma; low-dose cardioselective agents can be used with care in patients with bronchospasm or chronic lung disease or chronic smoking. In angina and hypertension, cardioselective agents are just as effective as

noncardioselective agents. In AMI complicated by stress-induced hypokalemia, nonselective blockers theoretically should be better antiarrhythmics than β_1-selective blockers.

Vasodilating β-blockers.

Carvedilol and nebivolol are the prototypes (see Fig. 1-10). These agents could have added value in the therapy of hypertension by achieving vasodilation and, in the case of nebivolol, better reduction of LVH is claimed.[98]

Antiarrhythmic β-blockers.

All β-blockers are potentially antiarrhythmic by virtue of Class II activity (see Fig. 1-6). Sotalol is a unique β-blocker with prominent added Class III antiarrhythmic activity (see Fig. 1-6; Chapter 8).

Pharmacokinetic properties of β-blockers

Plasma half-lives.

Esmolol, given intravenously, has the shortest of all half-lives at only 9 min. Esmolol may therefore be preferable in unstable angina and threatened infarction when hemodynamic changes may call for withdrawal of β-blockade. The half-life of propranolol (Table 1-3) is only 3 hours, but continued administration saturates the hepatic process that removes propranolol from the circulation; the active metabolite 4-hydroxypropranolol is formed, and the effective half-life then becomes longer. The biological half-life of propranolol and metoprolol (and all other β-blockers) exceeds the plasma half-life considerably, so that twice-daily dosages of standard propranolol are effective even in angina pectoris. Clearly, the higher the dose of any β-blocker, the longer the biologic effects. Longer-acting compounds such as nadolol, sotalol, atenolol, and slow-release propranolol (Inderal-LA) or extended-release metoprolol (Toprol-XL) should be better for hypertension and effort angina.

Table 1-3   -- Properties of Various β-Adrenoceptor Antagonist Agents, Nonselective Versus Cardioselective and Vasodilatory Agents

Generic Name (Trade Name)	Extra Mechanism	Plasma Half-Life (h)	Lipid Solubility	First-Pass Effect	Loss by Liver or Kidney	Plasma Protein Binding (%)	Usual Dose for Angina (Other Indications)	Usual Doses as Sole Therapy for Mild or Moderate Hypertension	Intravenous Dose (as Licensed In United States)
Noncardioselective									
Propranolol[†] (Inderal)	—	1-6	+++	++	Liver	90	80 mg 2× daily usually adequate (may give 160 mg 2× daily)	Start with 10-40 mg 2× daily. Mean 160-320 mg/day, 1-2 doses	1-6 mg
(Inderal-LA)	—	8-11	+++	++	Liver	90	80-320 mg 1× daily	80-320 mg 1× daily	—
Carteolol* (Cartrol)	ISA +	5-6	0/ +	0	Kidney	20-30	(Not evaluated)	2.5-10 mg single dose	—
Nadolol[†] (Corgard)	—	20-24	0	0	Kidney	30	40-80 mg 1× daily; up to 240 mg	40-80 mg/day 1× daily; up to 320 mg	—
Penbutolol (Levatol)	ISA +	20-25	+++	++	Liver	98	(Not studied)	10-20 mg daily	—
Sotalol[‡] (Betapace; Betapace AF)	—	7-18 (mean 12)	0	0	Kidney	5	(80-240 mg 2× daily in two doses for serious ventricular arrhythmias; up to 160 mg 2× daily for atrial fib, flutter)	80-320 mg/day; mean 190 mg	—
Timolol* (Blocadren)	—	4-5	+	+	L, K	60	(post-AMI 10 mg 2× daily)	10-20 mg 2× daily	—
Cardioselective									

Generic Name (Trade Name)	Extra Mechanism	Plasma Half-Life (h)	Lipid Solubility	First-Pass Effect	Loss by Liver or Kidney	Plasma Protein Binding (%)	Usual Dose for Angina (Other Indications)	Usual Doses as Sole Therapy for Mild or Moderate Hypertension	Intravenous Dose (as Licensed In United States)
Acebutolol* (Sectral)	ISA ++	8-13 (diacetolol)	0 (diacetolol)	++	L, K	15	(400-1200 mg/day in 2 doses for PVC)	400-1200 mg/day; can be given as a single dose	—
Atenolol[†] (Tenormin)	—	6-7	0	0	Kidney	10	50-200 mg 1× daily	50-100 mg/day 1× daily	5 mg over 5 min; repeat 5 min later
Betaxolol* (Kerlone)	—	14-22	++	++	L, then K	50	—	10-20 mg 1× daily	—
Bisoprolol* (Zebeta)	—	9-12	+	0	L, K	30	10 mg 1× daily (not in US) (HF, see Table 1-2)	2.5-40 mg 1× daily (see also Ziac)	—
Metoprolol[†] (Lopressor)	—	3-7	+	++	Liver	12	50-200 mg 2× daily (HF, see Table 1-2)	50-400 mg/day in 1 or 2 doses	5 mg 3× at 2 min intervals
Vasodilatory β-Blockers, Nonselective									
Labetalol* (Trandate) (Normodyne)	—	6-8	+++	++	L, some K	90	As for hypertension	300-600 mg/day in 3 doses; top dose 2400 mg/day	Up to 2 mg/min, up to 300 mg for severe HT
Pindolol* (Visken)	ISA +++	4	+	+	L, K	55	2.5-7.5 mg 3× daily (In UK, not US)	5-30 mg/day 2× daily	—
Carvedilol* (Coreg)	β1-, β2-, α-block; metabolic	6	+	++	Liver	95	(US, UK for heart failure) Angina in UK: up to 25 mg 2× daily	12.5-25 mg 2× daily	—
Vasodilatory β-Blockers, Selective									
Nebivolol (Bistolic in USA; Nebilet in UK)	NO-vaso-dilation; metabolic	10 (24 h, metabolites)	+++	+++ (genetic variation)	L, K	98	Not in UK or US (in UK, heart failure, adjunct in older adults)	5 mg once daily; 2.5 mg in renal disease or older adults	—

AMI, Acute myocardial infarction; *FDA,* Food and Drug Administration; *fib,* fibrillation; *HF,* heart failure; *HT,* hypertension; *ISA,* intrinsic sympathomimetic activity; *K,* kidney; *L,* liver; *NO,* nitric oxide; *PVC,* premature ventricular contractions.

§ Octanol-water distribution coefficient (pH 7.4, 37o C) where 0 = <0.5; + = 0.5-2; ++ = 2-10; +++ = >10

* Approved by FDA for hypertension.

† Approved for angina pectoris.

‡ Approved for life-threatening ventricular tachyarrhythmias.§ Metabolic, insulin sensitivity increased.

Protein binding.

Propranolol is highly bound, as are pindolol, labetalol, and bisoprolol. Hypoproteinemia calls for lower doses of such compounds.

First-pass liver metabolism.

First-pass liver metabolism is found especially with the highly lipid-soluble compounds, such as propranolol, labetalol, and oxprenolol. Major hepatic clearance is also found with acebutolol, nebivolol, metoprolol, and timolol. First-pass metabolism varies greatly among patients and alters the dose required. In liver disease or low-output states the dose should be decreased. First-pass metabolism produces active metabolites with, in the case of propranolol, properties different from those of the parent compound. Metabolism of metoprolol occurs predominantly via cytochrome P450 2D6–mediated hydroxylation and is subject to marked genetic variability.[93] Acebutolol produces large amounts of diacetolol, and is also cardioselective with ISA, but with a longer half-life and chiefly excreted by the kidneys (Fig. 1-11). Lipid-insoluble hydrophilic compounds (atenolol, sotalol, nadolol) are excreted only by the kidneys (see Fig. 1-11) and have low brain penetration. In patients with renal or liver disease, the simpler pharmacokinetic patterns of lipid-insoluble agents make dosage easier. As a group, these agents have low protein binding (see Table 1-3).
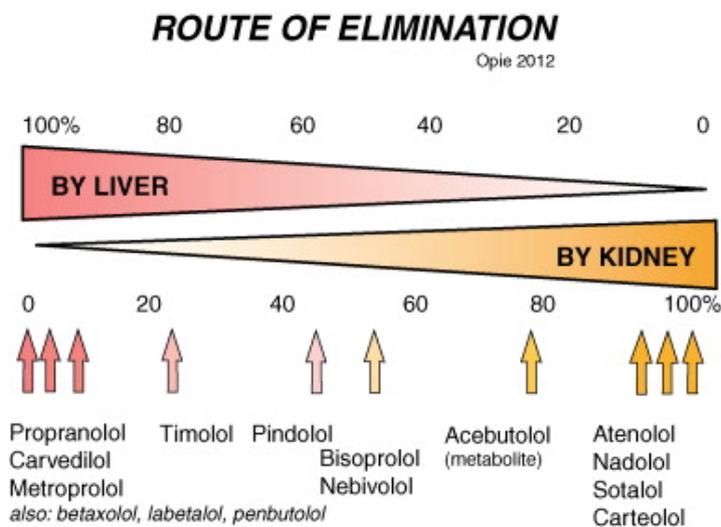
Figure 1-11 Comparative routes of elimination of β-blockers. Those most hydrophilic and least lipid-soluble are excreted unchanged by the kidneys. Those most lipophilic and least water-soluble are largely metabolized by the liver. Note that the metabolite of acebutolol, diacetolol, is largely excreted by the kidney, in contrast to the parent compound. (For derivation of data in figure, see third edition. Estimated data points for acebutolol and newer agents added.)
(Figure © L. H. Opie, 2012.)

Pharmacokinetic interactions.

Those drugs metabolized by the liver and hence prone to hepatic interactions are metoprolol, carvedilol, labetalol, and propranolol, of which metoprolol and carvedilol are more frequently used. Both are metabolized by the hepatic CYP2D6 system that is inhibited by paroxetine, a widely used antidepressant that is a selective serotonin reuptake inhibitor. To avoid such hepatic interactions, it is simpler to use those β-blockers not metabolized by the liver (see Fig. 1-11). β-blockers, in turn, depress hepatic blood flow so that the blood levels of lidocaine increase with greater risk of lidocaine toxicity.

Concomitant diseases and choice of β-blocker

Respiratory disease.

Cardioselective β$_1$-blockers in low doses are best for patients with reversible bronchospasm. In patients with a history of asthma, no β-blocker can be considered safe.

Associated cardiovascular disease.

For *hypertension plus effort angina,* see "β-blockers for hypertension" earlier in this chapter. In patients with *sick sinus syndrome,* pure β-blockade can be dangerous. Added ISA may be best. In patients with *Raynaud phenomenon,* propranolol with its peripheral vasoconstrictive effects is best avoided. In active *peripheral vascular disease,* β-blockers are generally contraindicated, although the evidence is not firm.

Renal disease.

The logical choice should be a β-blocker eliminated by the liver rather than the kidney (see Fig. 1-11). Of those, the vasodilating β-blocker nebivolol conserved the estimated glomerular filtration rate in patients with heart failure better than did metoprolol.[99]

Diabetes mellitus.

In diabetes mellitus, the risk of β-blockade in insulin-requiring diabetics is that the symptoms of hypoglycemia might be masked. There is a lesser risk with the cardioselective agents. In type 2 diabetics with hypertension, initial β-blocker therapy by atenolol was as effective as the ACE inhibitor, captopril, in reducing macrovascular end points at the cost of weight gain and more antidiabetic medication.[47] Whether *diabetic nephropathy* benefits as much from treatment with β-blockade is not clear. ARBs and ACE inhibitors have now established themselves as agents of first choice in diabetic nephropathy (see Chapter 5, p. 136). Carvedilol combined with RAS blocker therapy in diabetic patients with hypertension results in better glycemic control and less insulin resistance than combination therapy that includes metoprolol.[100] Although better glycemic control should theoretically translate into fewer cardiovascular events and other adverse outcomes, the short-term nature of this study does not allow conclusions on outcomes.

Those at risk of new diabetes.

The β-blocker and diuretics pose a risk of new diabetes,[35] which should be lessened by a truly low dose of the diuretic or by using another combination. Regular blood glucose checks are desirable.

Side effects of β-blockers

The *four major mechanisms for β-blocker side effects* are (1) smooth muscle spasm (bronchospasm and cold extremities), (2) exaggeration of the cardiac therapeutic actions (bradycardia, heart block, excess negative inotropic effect), (3) central nervous system penetration (insomnia, depression), and (4) adverse metabolic side effects. The *mechanism of fatigue* is not clear. When compared with propranolol, however, it is reduced by use of either a cardioselective β-blocker or a vasodilatory agent, so that both central and peripheral hemodynamic effects may be involved. When patients are appropriately selected, double-blind studies show no differences between a cardioselective agent such as atenolol and placebo. This may be because atenolol is not lipid soluble and should have lesser effects on bronchial and vascular smooth muscle than propranolol. When *propranolol* is given for hypertension, the rate of serious side effects (bronchospasm, cold extremities, worsening of claudication) leading to withdrawal of therapy is approximately 10%.[101] The rate of withdrawal with atenolol is considerably lower (approximately 2%), but when it comes to dose-limiting side effects, both agents can cause cold extremities, fatigue, dreams, worsening claudication, and bronchospasm. Increasing heart failure remains a potential hazard when β-blockade therapy is abruptly started at normal doses in a susceptible patient and not tailored in.

Central side effects.

An attractive hypothesis is that the lipid-soluble β-blockers (epitomized by propranolol) with their high brain penetration are more likely to cause central side effects. An extremely detailed comparison of propranolol and atenolol showed that the latter, which is not lipid soluble, causes far fewer central side effects than does propranolol.[102] However, depression remains an atenolol risk.[42] The lipid-solubility hypothesis also does not explain why metoprolol, which is moderately lipid soluble, appears to interfere less with some complex psychological functions than does atenolol and may even enhance certain aspects of psychological performance.[103]

Quality of life and sex life.

In the first quality-of-life study reported in patients with hypertension, propranolol induced considerably more central effects than did the ACE inhibitor captopril.[104] More modern β-blockers, with different fundamental properties, all leave the quality of life largely intact in hypertensives. However, there are a number of negatives. First, *weight gain* is undesirable and contrary to the lifestyle pattern required to limit cardiovascular diseases, including the metabolic syndrome and hypertension. Second, β-blockade may precipitate *diabetes,*[50] a disease that severely limits the quality of life. Third, during *exercise,* β-blockade reduces the total work possible by approximately 15% and increases the sense of fatigue. Vasodilatory β-blockers may be exceptions but lack outcome studies in hypertension. *Erectile dysfunction* is an age-dependent complication of β-blockade. In a large group with mean age 48 years, erectile problems took place in 11% given a β-blocker, compared with 26% with a diuretic and 3% with placebo.[105] β-blockers have consistently impaired sexual intercourse more than an ACE inhibitor or ARB, the latter improving sexual output.[106] Changing to nebivolol may improve erections.[107] Sildenafil (Viagra) or similar agents should also help, but are relatively contraindicated if the β-blocker is used for angina (because of the adverse interaction with nitrates, almost always used in those with angina).

Adverse metabolic side effects and new diabetes.

The capacity of β-blockers to increase new diabetes, whether given for hypertension or postinfarct,[35] comes at a time when diabetes is increasingly recognized as major cardiovascular hazard (see Chapters 7 and 11). A wise precaution is to obtain fasting blood glucose levels and, if indicated, a glucose tolerance curve before the onset of chronic β-blockade and at annual intervals during therapy. Note that the vasodilatory β-blockers carvedilol and nebivolol both promote formation of nitric oxide and both have a better metabolic profile than comparator cardioselective agents, without, however, long-term outcome data in hypertension (see "Specific β-Blockers" later in this chapter).

Contraindications to β-blockade

The absolute contraindications to β-blockade can be deduced from the profile of pharmacologic effects and side effects (Table 1-4). Cardiac absolute contraindications include severe bradycardia, preexisting high-degree heart block, sick sinus syndrome, and overt LV failure unless already conventionally treated and stable (Fig. 1-12). Pulmonary contraindications are overt asthma or severe bronchospasm; depending on the severity of the disease and the cardioselectivity of the β-blocker used, these may be absolute or relative contraindications. The central nervous system contraindication is severe depression (especially for propranolol). Active peripheral vascular disease with rest ischemia is another contraindication. The metabolic syndrome suggests caution.

Table 1-4   -- β-Blockade: Contraindications and Cautions

(Note: cautions may be overridden by the imperative to treat, as in postinfarct patients)
Cardiac
Absolute: Severe bradycardia, high-degree heart block, cardiogenic shock, overt untreated left ventricular failure (versus major use in early or stabilized heart failure).
Relative: Prinzmetal's angina (unopposed α-spasm), high doses of other agents depressing SA or AV nodes (verapamil, diltiazem, digoxin, antiarrhythmic agents); in angina, *avoid sudden withdrawal*.
Pulmonary
Absolute: Severe asthma or bronchospasm. Must question for past or present asthma. Risk of fatalities.
Relative: Mild asthma or bronchospasm or chronic airways disease. Use agents with cardioselectivity plus β_2-stimulants (by inhalation).
Central Nervous
Absolute: Severe depression (especially avoid propranolol).
Relative: Vivid dreams: avoid highly lipid-soluble agents (see Fig. 1-11) and pindolol; avoid evening dose. Visual hallucinations: change from propranolol. Fatigue (all agents). If low cardiac output is cause of fatigue, try vasodilatory β-blockers. Erectile dysfunction may occur (check for diuretic use; consider change to nebivolol and/or ACE inhibitor/ARB). Psychotropic drugs (with adrenergic augmentation) may adversely interact.
Peripheral Vascular, Raynaud Phenomenon
Absolute: Active disease: gangrene, skin necrosis, severe or worsening claudication, rest pain.
Relative: Cold extremities, absent pulses, Raynaud phenomenon. Avoid nonselective agents (propranolol, sotalol, nadolol); prefer vasodilatory agents.
Diabetes Mellitus
Relative: Insulin-requiring diabetes: nonselective agents decrease reaction to hypoglycemia; use selective agents. Note successful use of atenolol in type 2 diabetes in prolonged UK trial at cost of weight gain and more antidiabetic drug usage.
Metabolic Syndrome or Prediabetes
β-blockers may increase blood sugar by 1-1.5 mmol/L and impair insulin sensitivity especially with diuretic co-therapy; consider use of carvedilol or nebivolol.
Renal Failure
Relative: As renal blood flow falls, reduce doses of agents eliminated by kidney (see Fig. 1-11).
Liver Disease
Relative: Avoid agents with high hepatic clearance (propranolol, carvedilol, timolol, acebutolol, metoprolol). Use agents with low clearance (atenolol, nadolol, sotalol). See Fig 1-11. If plasma proteins low, reduce dose of highly bound agents (propranolol, pindolol, bisoprolol).

Pregnancy Hypertension
β-blockade increasingly used but may depress vital signs in neonate and cause uterine vasoconstriction. Labetalol and atenolol best tested. Preferred drug: methyldopa.
Surgical Operations
β-blockade may be maintained throughout, provided indication is not trivial; otherwise stop 24 to 48 hours beforehand. May protect against anesthetic arrhythmias and perioperative ischemia. Preferred intravenous drug: esmolol. Use atropine for bradycardia, β-agonist for severe hypotension.
Age
β-blockade often helps to reduce BP, but lacks positive outcome data. Watch pharmacokinetics and side effects in all older adult patients.
Smoking
In hypertension, β-blockade is less effective in reducing coronary events in smoking men.
Hyperlipidemia
β-blockers may have unfavorable effects on the blood lipid profile, especially nonselective agents. Triglycerides increase and HDL-cholesterol falls. Clinical significance unknown, but may worsen metabolic syndrome. Vasodilatory agents, with intrinsic sympathomimetic activity or α-blocking activity, may have mildly favorable effects.

Adapted from Kjeldssen, LIFE elderly substudy, JAMA 2002;288:1491.

ACE, Angiotensin-converting enzyme; *AV,* atrioventricular; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *HDL,* high-density lipoprotein; *SA,* sinoatrial.
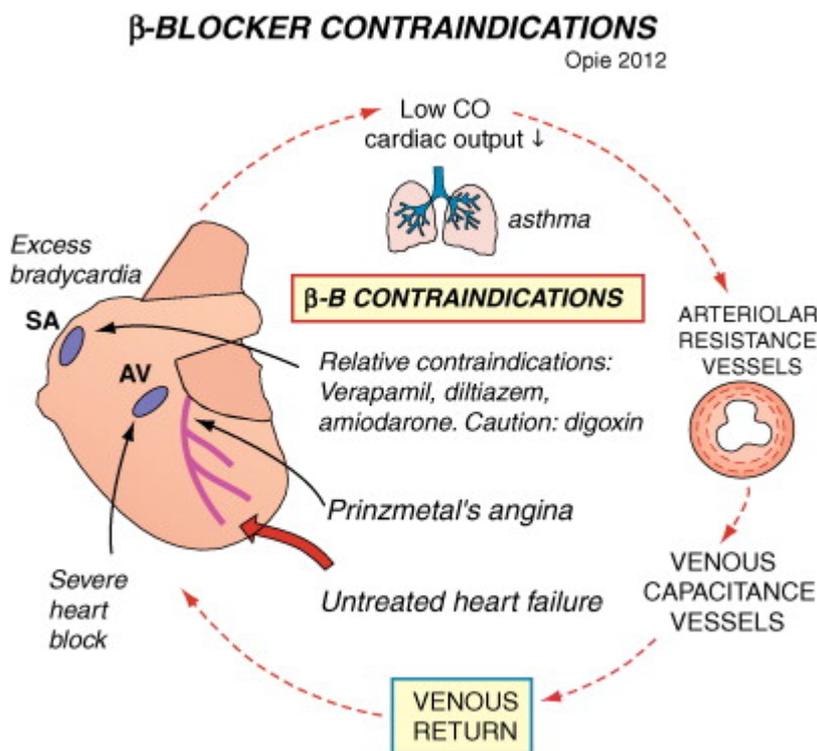
Figure 1-12 Contraindications to β-blockade. Metabolic syndrome (not shown) is a relative contraindication to β-blockade for hypertension.
(Figure © L. H. Opie, 2012.)

DRUGS FOR THE HEART
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Overdose of β-blockers

Bradycardia may be countered by intravenous atropine 1 to 2 mg; if serious, temporary transvenous pacing may be required. When an infusion is required, glucagon (2.5 to 7.5 mg/h) is logical because it stimulates formation of cAMP by bypassing the occupied β-receptor. However, evidence is only anecdotal.[108] Logically an infusion of a phosphodiesterase inhibitor, such as amrinone or milrinone, should help cAMP to accumulate. Alternatively, dobutamine is given in doses high enough to overcome the competitive β-blockade (15 mcg/kg/min). In patients without ischemic heart disease, an infusion (up to 0.10 mcg/kg/min) of isoproterenol may be used.

Specific β-blockers

Of the large number of β-blockers, the ideal agent for hypertension or angina might have (1) advantageous pharmacokinetics (simplicity, agents not metabolized in liver); (2) a high degree of cardioselectivity (bisoprolol); (3) long duration of action (several); and (4) a favorable metabolic profile, especially when associated with vasodilatory properties (carvedilol and nebivolol).

Propranolol *(Inderal)* is the historical gold standard because it is licensed for so many different indications, including angina, acute-stage MI, postinfarct follow-up, hypertension, arrhythmias, migraine prophylaxis, anxiety states, and essential tremor. However, propranolol is not β_1-selective. Being lipid soluble, it has a high brain penetration and undergoes extensive hepatic first-pass metabolism. Central side effects may explain its poor performance in quality-of-life studies. Propranolol also has a short half-life so that it must be given twice daily unless long-acting preparations are used. The chief of the other agents are dealt with alphabetically.

Acebutolol *(Sectral)* is the cardioselective agent with ISA that gave a good quality of life in the 4-year TOMH study in mild hypertension. In particular, the incidence of impotence was not increased.[109]

Atenolol *(Tenormin)* was one of the first of the cardioselective agents and now in generic form is one of the most widely used drugs in angina, in postinfarct protection, and in hypertension. However, its use as first-line agent in hypertension is falling into disfavor,[110] with poor outcomes, including increased all-cause mortality when compared with the CCB amlodipine in ASCOT.[34] There are very few trials with outcome data for atenolol in other conditions, with two exceptions: the ASIST study in silent ischemia[15] and INVEST in hypertensives with coronary artery disease. Here atenolol had equality of major clinical outcomes with verapamil at the cost of more episodes of angina, more new diabetes, and more psychological depression.[41],[111] Note that atenolol was often combined with a diuretic and verapamil with an ACE inhibitor. In the British Medical Research Council trial of hypertension in older adults, atenolol did not reduce coronary events.[88] More recently, atenolol was inferior to the ARB losartan in the therapy of hypertensives with LVH.[112]

Bisoprolol *(Zebeta in the United States, Cardicor or Emcor in the United Kingdom)* is a highly β_1-selective agent, more so than atenolol, licensed for hypertension, angina heart failure in the United Kingdom but only for hypertension in the United States. It was the drug used in the large and successful CIBIS-2 study in heart failure, in which there was a large reduction not only in total mortality but also in sudden death.[113] In CIBIS-3, bisoprolol compared well with enalapril as first-line agent in heart failure.[80] A combination of low-dose bisoprolol and low-dose hydrochlorothiazide (Ziac) is available in the United States (see Combination Therapy on page 11).

Carvedilol *(Coreg in the United States, Eucardic in the United Kingdom)* is a nonselective vasodilator α-β-blocker with multimechanism vasodilatory properties mediated by antioxidant activity, formation of nitric oxide, stimulation β-arrestin-MAP-kinase[65] and α-receptors, that has been extensively studied in CHF[61] and in postinfarct LV dysfunction.[29] Metabolically, carvedilol may increase insulin sensitivity.[49] In the United States, it is registered for hypertension, for CHF (mild to severe), and for post-MI LV dysfunction (EF ≤ 40%), but not for angina.

Labetalol *(Trandate, Normodyne)* is a combined α- and β-blocking antihypertensive agent that has now largely been supplanted by carvedilol except for acute intravenous use as in hypertensive crises (see Table 7-4 on page 261).

Metoprolol *(Toprol-XL)* is cardioselective and particularly well studied in AMI and in postinfarct protection. Toprol-XL is approved in the United States for stable symptomatic Class 2 or 3 heart failure.[114] It is also registered for hypertension and angina. *Lopressor, shorter acting,* is licensed for angina and MI.

Nadolol *(Corgard)* is very long acting and water soluble, although it is nonselective. It is particularly useful

when prolonged antianginal activity is required.

Nebivolol *(Nebilet in the United Kingdom, Bystolic in the United States)* is a highly cardioselective agent with peripheral vasodilating properties mediated by nitric oxide.[6] Hepatic metabolites probably account for the vasodilation[115] and the long biological half-life.[116] Nebivolol reverses endothelial dysfunction in hypertension, which may explain its use for erectile dysfunction in hypertensives.[107] There are also metabolic benefits. In a 6-month study, nebivolol, in contrast to atenolol and at equal BP levels, increased insulin sensitivity and adiponectin levels in hypertensives.[117] Nebivolol given in the SENIORS trial to older adult patients with a history of heart failure or an EF of 35% or less reduced the primary composite end-point of all-cause mortality and cardiovascular hospitalizations, also increasing the EF and reducing heart size.[78]

Penbutolol *(Levatol)* has a modest ISA, similar to acebutolol, but is nonselective. It is highly lipid-soluble and is metabolized by the liver.

Sotalol *(Betapace, Betapace AF)* is a unique nonselective β-blocker that has Class 3 antiarrhythmic activity. It is licensed for life-threatening ventricular arrhythmias as Betapace, and now also as Betapace AF for maintenance of sinus rhythm in patients with symptomatic atrial fibrillation or atrial flutter. Sotalol is a water-soluble drug, excreted only by the kidneys, so that Betapace AF is contraindicated in patients with a creatinine clearance of less than 40 mL/min.

Timolol *(Blocarden)* was the first β-blocker shown to give postinfarct protection and it is one of the few licensed for this purpose in the United States. Other approved uses are for hypertension and in migraine prophylaxis.

Ultrashort-acting intravenous β-blockade

Esmolol *(Brevibloc)* is an ultrashort-acting $β_1$-blocker with a half-life of 9 minutes, rapidly converting to inactive metabolites by blood esterases. Full recovery from β-blockade occurs within 30 minutes in patients with a normal cardiovascular system. *Indications* are situations in which on-off control of β-blockade is desired, as in SVT in the perioperative period, or sinus tachycardia (noncompensatory), or emergency hypertension in the perioperative period (all registered uses in the United States). Other logical indications are emergency hypertension (pheochromocytoma excluded) or in unstable angina.[118] *Doses* are as follows: For *SVT,* loading by 500 mcg/kg/min over 1 minute, followed by a 4-minute infusion of 50 mcg/kg/min (US package insert). If this fails, repeat loading dose and increase infusion to 100 mcg/kg/min (over 4 minutes). If this fails, repeat loading dose and then infuse at rates up to 300 mcg/kg/min. Thereafter, to maintain control, infuse at adjusted rate for up to 24 hours. For *urgent perioperative hypertension,* give 80 mg (approximately 1 mg/kg) over 30 seconds and infuse at 150 to 300 mcg/kg/min if needed. For more gradual control of BP, follow routine for SVT. Higher doses are usually required for BP control than for arrhythmias. After the emergency, replace with conventional antiarrhythmic or antihypertensive drugs. For *older adult patients with non-ST elevation MI* requiring acute β-blockade despite symptoms of heart failure, a cautious infusion of 50-200 mcg/kg/min may be tried.[119] *Cautions* include extravasation of the acid solution with risk of skin necrosis.

From the past, into the future

Predictions are often wrong. Nonetheless, trends can be identified, looking both backward and forward (Fig. 1-13). Originally, β-blockers were created by Sir James Black in 1962 to counter adrenergic stimulation in effort angina, for which he later received the Nobel Prize. In 1964 Brian Prichard discovered the antihypertensive properties. In 1975 Waagstein and Hjalmarson showed clinical improvement following β-blockade in seven patients with advanced congestive cardiomyopathy. In 1981 the Norwegian Study Group reported a major benefit for β-blockade in postinfarct patients. In 1986 in ISIS-1, a ground-breaking mega-trial on AMI, the Oxford group of Peter Sleight found that acute β-blockade diminished postinfarct mortality. Currently, use in uncomplicated hypertension as first-line agent is under challenge. Projecting into the future, evidence-based use of β-blockade will be optimal in heart failure and in postinfarct patients, with a slight decline in angina as metabolic agents come into greater use. There already is and there will be a greater trend away from β-blockers as agents of first choice in uncomplicated hypertension.
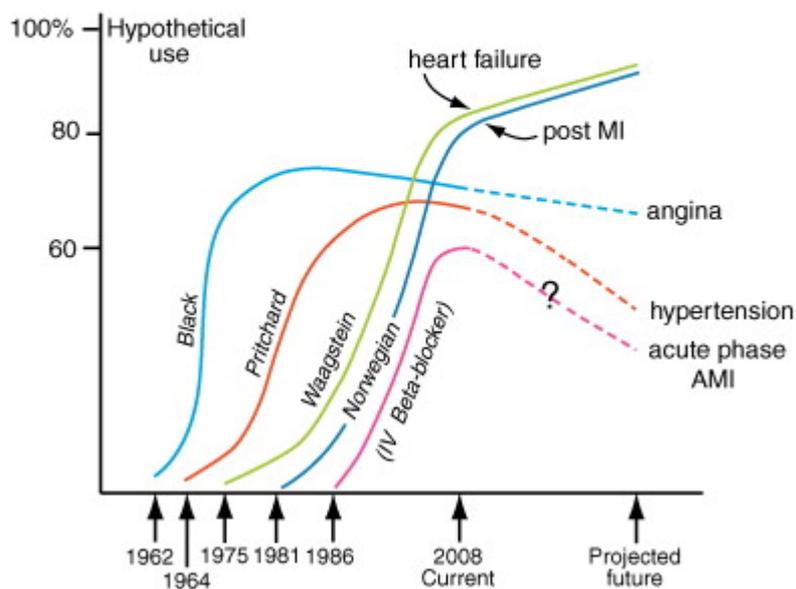
Figure 1-13 Hypothetical patterns of change of β-blocker use over time. See text for details.
(Dr. J. D. Horowitz is thanked for discussions leading to this figure. Figure © J. D. Horowitz.)

Summary

1. **Despite some setbacks in recent hypertension trials,** β-blockers still come closest to providing all-purpose cardiovascular therapy with the conspicuous absence of any benefit for lipid problems. Licensed indications include angina, hypertension, AMI, postinfarct follow-up, arrhythmias, and now heart failure. Data for postinfarct protection and for mortality reduction in CHF are particularly impressive. Other data are less compelling (Table 1-5).

2. **In heart failure,** solid data support the essential and earlier use of β-blockers in stable systolic heart failure, to counter the excessive adrenergic drive. Only three agents have been studied in detail, namely carvedilol, metoprolol, and bisoprolol, of which only the first two are approved for heart failure in the United States. In older adults, nebivolol improved EF in systolic but not diastolic heart failure. Following the recommended protocol with slow, incremental doses of the chosen agent is essential.

3. **For coronary heart disease,** β-blockade is very effective symptomatic treatment, alone or combined with other drugs, in 70% to 80% of patients with classic effort angina. However, atenolol-based therapy was no better at lessening major outcomes than verapamil-based therapy, and worse for some minor outcomes. β-blockers are part of the essential postinfarct protection armamentarium. For ACSs, indirect evidence suggests a quadruple follow-up regime of aspirin, statin, ACE inhibitor, and β-blockade, but there are no compelling outcome trials. Overall, there is no clinical evidence that β-blockers slow the development of coronary artery disease.

4. **In hypertension** β-blockers have lost their prime position, although they reduce the BP effectively in 50% to 70% of those with mild to moderate hypertension. The crucial study showed that for equal brachial pressures, the aortic pressure was less reduced with atenolol than with the CCB amlodipine, which could explain why β-blockers reduce stroke less than several other agents. Older adults with hypertension, especially those of the black ethnic group, respond less well to β-blocker monotherapy. The previously recommended combination of β-blockers and diuretics may provoke new diabetes, with lesser risk if the diuretic dose is truly low.

5. **In arrhythmias** β-blockers are among the more effective ventricular antiarrhythmics.

6. **Metabolic side-effects,** including new diabetes, have come to the fore. β-blockers can be diabetogenic even without diuretics. The vasodilatory β-blockers carvedilol and nebivolol appear to be exceptions and have outcome studies only in heart failure.

7. **Is there still a role for propranolol?** There is no particular advantage for this original "gold standard" drug, with its poor quality-of-life outcomes, unless hypertension or angina with some other condition in which experience with propranolol is greater than with other β-blockers (e.g., POTS, hypertrophic cardiomyopathy, migraine prophylaxis, anxiety, or essential tremor) is also occurring.

8. **Other b-blockers** are increasingly used because of specific attractive properties: cardioselectivity (acebutolol, atenolol, bisoprolol, metoprolol), vasodilatory capacity and possible metabolic superiority (carvedilol and nebivolol), positive data in heart failure (carvedilol, metoprolol, bisoprolol, nebivolol) or postinfarct protection (metoprolol, carvedilol, timolol), lipid insolubility and no hepatic metabolism (atenolol, nadolol, sotalol), long action (nadolol) or long-acting formulations, ISA in selected patients to help avoid bradycardia (pindolol, acebutolol), and well-studied antiarrhythmic properties (sotalol). Esmolol is the best agent for intravenous use in the perioperative period because of its extremely short half-life.

9. **Evidence-based use** directs the use of those agents established in large trials because of the known doses and clearly expected benefits. For example, for postinfarct protection propranolol, metoprolol, carvedilol, and timolol are the best studied, of which only carvedilol has been studied in the reperfusion era. For stabilized heart failure, carvedilol, metoprolol, and bisoprolol have impressive data from large trials. Carvedilol especially merits attention, being licensed for a wide clinical range, from hypertension to LV dysfunction to severe heart failure, and having best trial data in heart failure. For arrhythmias, sotalol with its class III properties stands out.

Table 1-5   -- Summary of use of β-Blockers in Cardiovascular Disease

Conditions	Must Use* (Level A)	May Use (Level B)	Don't Use (Data Poor)
Heart failure	✔		
Post-MI	✔		
Arrhythmias (ventricular, post-MI)	✔		
Arrhythmias (others)		✔	
ACS, unstable angina (NSTE)		✔	
ACS, acute-phase MI		✔	
Stable angina without MI		✔	
Hypertension (initial choice)			Selective
Hypertension (selected)		✔	
Metabolic syndrome			Careful

For concepts, see reference 110.

Note: "Must use" can override "Don't use."

33 = strongly indicated; **3**= indicated.

ACS, Acute coronary syndrome; *MI,* myocardial infarction; *NSTE,* non-ST elevation.

* Unless contraindicated.

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