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Beta-blockers in the management of cardiovascular diseases

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Beta-blockers (β-blockers) are some of the most commonly prescribed therapeutic agents and are used for a wide variety of medical conditions. In addition to being commonly used in conditions such as high blood pressure, heart failure, acute coronary syndrome, and atrial fibrillation, β-blockers can also be useful when used perioperatively for noncardiac surgery. Recently, recommendations for perioperative use of β-blockers for patients undergoing noncardiac surgery have been updated. Although some pharmacological effects of β-blockers are class effects, others are specific to an individual agent. The effect of various β-blockers on lipid profiles is mixed and there does not seem to be a consistent class effect. For these reasons, therapeutic outcomes of β-blockers, when used for a certain pathologic process, may differ from one to another. In clinical practice, β-blockers are often either under-dosed or under-prescribed. The objective of this article is to discuss some of the clinically relevant evidenced-based research and clinical trials outcomes of commonly used β-blockers.

The use of beta-blockers (β-blockers) in clinical practice has been evolving for more than half a century. Currently, these medications are used for a number of medical conditions such as unstable angina (USA), acute myocardial infarction (AMI), heart failure (HF), hypertension (HTN), atrial fibrillation (AF), ventricular arrhythmias, migraine headache, hyperthyroidism, essential tremor, aortic dissection, social phobia, glaucoma, esophageal varices, and so on.[1-3] Despite the clear beneficial effects of β-blockers on morbidity and mortality in medical conditions, such as HF and stable post- AMI, they are often under-prescribed or under-dosed.[4,5] In patients with HTN, whether β-blockers should be among the first line of medications in the absence of compelling evidence is being questioned. Not all β-blockers are cardioprotective in stable HF patients with left venticular dysfunction. For other conditions such as peripheral vascular disease (PVD) and chronic obstructive pulmonary disease (COPD), there is not enough evidence to contradict the use of β-blockers (Table 1).[6,7]

Although some therapeutic effects of β-blockers can be attributed to its class, others are specific to an individual β-blocker not only because of the differences in their pharmacokinetic, pharmacodynamic, and intrinsic properties, but also owing to the difference in the genetic polymorphism of the patients.[8,9] In a recent meta-analysis, long-acting metoprolol, carvedilol, atenolol, and propranolol were compared with their respective brand-name counterparts for their pharmacological effectiveness. The study demonstrated that generic β-blockers and their brand-name counterparts did not differ significantly in the clinical outcomes tested. However, the clinical trials reviewed were done in healthy, small populations and for a short period of time, which suggests long-term outcomes would be similar but have yet to be demonstrated.[10]

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Table 1 SORT key recommendations for practice

Clinical recommendation	Evidence rating	References
Cardioselective β-blockers may be safely used in patients with COPD or asthma.	A	11,12
In the absence of compelling evidence, β-blockers should not be used as first-line monotherapy in hypertensive patients older than 60 years.	A	24-29
In the absence of contraindications, all patients with stable NYHA class II and III HF should be on a β-blocker (preferably carvedilol, bisoprolol, or metoprolol) with a target resting heart rate between 55 and 60 bpm.	A	32-37
β-blockers unless contraindicated should be used in all patients with stable and USA.	A	43-45
β-blockers have been shown to decrease morbidity and mortality if given in stable AMI patients and therefore should be routinely used unless contraindicated.	A	46,47
In patients with AF, β-blocker alone was as effective as digoxin or digoxin plus CCB but was more effective than CCB alone in rate control.	C	54-58

SORT Levels of Recommendation:
A = Recommendation based on consistent and good quality patient-oriented evidence.
B = Recommendation based on inconsistent or limited quality patient-oriented evidence.
C = Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, and case series for studies of diagnosis, treatment, prevention, or screening.
For more information about the SORT evidence rating system visit: http://www.aafp.org/online/en/home/publications/journals/afp/afpsort.html.

Table 2 lists β-blockers based on their receptor selectivity as cardioselective (atenolol, bisoprolol, metoprolol, nebivolol) and noncardioselective. Noncardioselective β-blockers are further subdivided into those with intrinsic sympathomimetic activity (ISA) (acebutolol, pindolol), those without ISA (nadolol, propranolol, sotalol), and those with alpha-adrenergic–blocking activities (carvedilol, labetalol). Cardioselective β-blockers bind mainly to β1-receptors, whereas nonselective β-blockers bind to both β1 and β2 receptors. At higher doses, cardioselective β-blockers bind to β2 receptors as well.

β-blockers and lipids

Effects of different β-blockers on the lipid profile are variable. In general, noncardioselective β-blockers without ISA increase serum triglyceride, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, and total cholesterol, and they decrease high-density lipoprotein. Cardioselective β-blockers and those with ISA have lesser effects on lipid profile. Acebutolol was found to be lipid-neutral. Pindolol, on the other hand, gave mixed results on lipid profile from being lipid-neutral to lipid-lowering. Carvedilol has been reported to increase insulin sensitivity and decrease triglycerides and increase high-density lipoprotein. Labetalol, which belongs to the same subgroup as carvedilol, was found to be neutral. When metoprolol was administered to nondiabetic hypertensive patients, insulin sensitivity was unchanged, high-density lipoprotein was decreased, and total cholesterol, triglyceride, and low-density lipoprotein were increased.[11,12]

β-blockers and HTN

Whether β-blockers should be used as a first-line agent in the absence of compelling indications in hypertensive patients is recently being questioned. Several clinical trials have tried to quantify the effects β-blocker on morbidity and mortality when used as the first-line antihypertensive therapy. A review of 13 clinical trials, with more than 91,000 subjects in which β-blockers were compared with placebo, diuretics, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB) concluded that β-blockers, when used as a first line therapy for HTN, were inferior to ACEI, ARB, and CCB in reducing some of the important outcomes measured. Although β-blockers were superior to placebo in reducing the risk of stroke, it did not change the all-cause mortality, incidence of coronary heart disease, or death from cardiovascular events. When compared with CCB, ACEI, and ARB, the effect of β-blockers on stroke was inferior. β-blockers were also inferior to CCBs in reducing cardiovascular events.[13]

A review of nine clinical trials in which atenolol was either compared with placebo (4 studies with 6825 patients) or with another antihypertensive agent (5 studies with 17,671 patients) concluded that, compared with placebo, atenolol was no better in reducing total mortality, cardiovascular mortality, myocardial infarction, and stroke. Compared with other antihypertensive therapy, patients in the atenolol group had higher mortality as well as cardiovascular mortality and stroke.[14]

A review of 18 randomized, clinical trials in which β-blockers were used as first-line treatment for HTN advised against the use of β-blockers as the first-line antihypertensive agent.[15] This was supported by another meta-analysis that reviewed 21 HTN trials involving 145,811 patients.[16] Outcomes of β-blockers also seemed to depend on the age of hypertensive patients. β-blockers, compared with placebo or other antihypertensive therapy, significantly reduced the composite outcome (death, stroke, or MI) in

Table 2 Classification and pharmacology of β-blockers

Selective	USFDA*-approved indications	Dose adjustment in renal disease	Dose adjustment in liver disease	Off-label use	Comments
Atenolol	HTN, angina, post-MI	Yes. Dialyzable. In patients with CrCl <15, maximum recommended dose is 25 mg/day.	No	Acute ethanol withdrawal, supraventricular and ventricular tachycardia.	Not very effective in migraine prophylaxis. It may be taken with or without food.
Bisoprolol	HTN	Not dialyzable, but dose adjustment is recommended in renal impairment.	Yes. Start with 2.5/day and maximum daily dose is 10 mg.	USA, post-AMI, HF, hyperthyroidism, migraine prophylaxis, and anxiety.	More β1-selctive than atenolol and metoprolol. Binds to β2-receptors at dose higher than 20 mg/day.
Metoprolol	HTN, HF, chronic USA	Advised to decrease dose although there are no data support it.	No specific guideline.	Migraine.	Binds to β2-adrenergic receptors at a dose higher than 100 mg/day. Food increases the absorption of regular metoprolol but not of extended-release tablet.
Nebivolol	HTN	Yes. CrCl <30 mL/min, start with 2.5 mg/day.	Recommended to use lower daily dose.	HF, migraine.	Selective β1-blocker Binds to β2-receptors at a dose higher than 10 mg/day. Causes vasodilatation through endothelium-derived nitric oxide production. Food does not interfere with absorption.
Nonselective without ISA					
Nadolol	HTN, USA	Yes	No		Not metabolized by liver. Excreted unchanged in the urine.
Propranolol	HTN, USA, essential tremor, migraine prophylaxis, IHSS, cardiac dysrhythmias, post-AMI, adjunct in pheochromocytoma.	No	Yes		Sublingual administration and food increase the bioavailability, and cigarette smoking decreases it.
Sotalol	AF, tachyarrhythmia, atrial flutter.	Yes. Contraindicated in patients with CrCl <40 mL/min.	No	Angina	Class II and III β-blocker. Because of pro-rhythmic nature, initiation and any dose adjustment should be done only under careful cardiac monitoring.
Nonselective with ISA					
Acebutolol	HTN, ventricular arrhythmias.	Yes. If CrCl is between 25 and 49, reduce dose by 50%. If CrCl is <25, reduce dose by 75%.	Use with caution.	Angina, syncope, myocardial re-infarction.	May be taken with or without food.
Pindolol	HTN	Yes	Yes		
Nonselective with α-adrenergic blocking activity					
Carvedilol	HTN, HF, post-MI .	No. Does not cross dialysis membrane.	Dose reduction by about 20% is recommended.	Chronic USA, atrial arrhythmia.	At high dose has calcium channel blocking. Because of vasodilatory effects, elderly patients are at risk for orthostatic hypotension and even syncope.[20] Has been reported to decrease microalbuminuria.[21,22]
Labetalol	HTN	No. Not removed by hemo- or peritoneal dialysis.	Decrease dose.	α-Blockers.	

USFDA, United States Food and Drug Administration; *CrCl*, creatinine clearance; HTN, hypertension; HF, heart failure; MI, myocardial infarction; USA, unstable angina; AMI; acute myocardial infarction.

hypertensive patients younger than 60 years of age. In older patients, β-blockers were able to reduce the incidence of stroke and HF but had no significant impact on rates of MI or death when compared with placebo. When compared with other antihypertensive agents, β-blockers were associated with a higher risk of stroke.[17]

Results from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial have shown that losartan was significantly better in reducing incidence of fatal or nonfatal stroke compared with atenolol in high-risk patients (HTN comorbid with diabetes, cardiovascular disease, left ventricular hypertrophy, and/or isolated systolic HTN) with HTN. A significant number of patients (77%) in the losartan group had a regression of left ventricular hypertrophy compared with the atenolol group. The fall in blood pressure in those two groups was similar (30.2/16.6 losartan vs. 29.1/16.1 atenolol). The LIFE trial also cautioned about an apparent increase in incidence of new-onset diabetes that was associated with atenolol vs. losartan (8.0% vs. 6.0%, $P < 0.001$).[18]

Data from the Medical Research Council (MRC) trial in which hydrochlorothiazide [HCTZ] plus amiloride was compared with atenolol in elderly hypertensive patients suggested that HCTZ and amiloride were superior to atenolol in improving coronary events and cardiovascular or all-cause mortality events. Reduction in the cerebrovascular incidence was noticeable in the diuretics group (31%, $P = 0.04$) as well as the diuretics plus atenolol group (25%, $P = 0.04$). Atenolol alone showed an insignificant decrease in the rate of cerebrovascular events when compared with placebo (9% vs. 10.8%).[19]

The Anglo-Scandinavian Cardiac Outcome Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) included 19,257 high-risk patients with HTN and randomized them to either the amlodipine or atenolol groups. After five and half years of follow-up, the trial was stopped early when the atenolol group showed less cardiovascular benefit, higher stroke, and more mortality compared with the amlodipine group (HR 0.77 vs. 0.86).[20] Whether metoprolol, bisoprolol, or carvedilol are superior to atenolol in preventing adverse cardiovascular events in high-risk hypertensive patients remains to be elucidated. In the International Verapamil-Trandolapril Study (INVEST) there was no difference between the atenolol and verapamil groups in the incidence of primary (death, nonfatal myocardial infarction, nonfatal stroke) or secondary outcomes.[21]

Table 3 summarizes results from some the clinical trials where β-blockers were compared with other antihypertensive agents. Current evidence based on several clinical trials (CAPPP, STOP-Hypertension-2, NORDIL, LIFE, ASCOT-BPLA)[22-24] and meta-analysis does not support the use of β-blocker as first-line therapy in the treatment of HTN in patients older than 60 years of age in the absence of compelling indications (previous MI, HF, AF, frequent migraine headache).[25-27] To date, there is no recommendation for whether atenolol should be replaced by another β-blocker or even if β-blockers in general should be used as a first- or second-line antihypertensive therapy in the absence of compelling indication. More clinical trials are needed to determine whether newer β-blockers nebivolol or carvedilol reduce the composite outcome (stroke, MI, or death) in hypertensive patients.

β-blockers and HF

ACEIs and β-blockers are first-line therapy for HF patients with left ventricular dysfunction. β-blockers, at least in part by decreasing the activation of the sympathetic nervous

Table 3 Hypertension and β-blocker clinical trials

Trials	Drugs tested	Conclusions	Ref
CAPPP	Captopril β-blocker and/or diuretic	No difference in cardiovascular events except in diabetic patients; captopril was superior in patients with HTN	24
INVEST	Verapamil Atenolol	No difference in primary or secondary outcomes in patients with HTN	62
LIFE	Losartan Atenolol	Losartan better than atenolol in reducing fatal or nonfatal stroke, regression of LVH in patients with HTN	18
	Atenolol Amlodipine	Amlodipine superior to atenolol in lowering nonfatal MI, fatal coronary events, strokes, all-cause mortality, lower incidence of diabetes	20
MRC	Propranolol Atenolol HCTZ Amiloride	β-blockers did not reduce coronary events or cardiovascular or all-cause mortality, where as diuretic did	18
NORDIL	β-blocker, diuretics, or both Diltiazem	Same as STOP-Hypertension-2 trial	23
STOP-Hypertension-2	Lisinopril, enalapril, felodipine, isradipine, diuretic β-blockers	Similar benefit between all drugs on fatal or nonfatal-stroke, MI, and other cardiovascular mortality	22

MRC, Medical Research Council; *STOP*, Swedish Trial in Old Patients with Hypertension; *NORDIL*, Nordic Diltiazem Study; *LIFE*, Losartan Intervention Endpoint Reduction in Hypertension; *ASCOT-BPLA*, Anglo-Scandinavian Cardiac Outcome Trial–Blood Pressure Lowering Arm; *INVEST*, International Verapamil-Trandolapril Study; *CAPPP*, Captopril Prevention Project; *HCTZ*, Hydrochlorothiazide.

Table 4 Heart failure and β-blocker clinical trials

Clinical trials	Drugs tested (target dose)	Trial outcomes	Ref
BEST trial	Bucindolol	Reduced only cardiovascular mortality. No reduction in other causes of mortality evaluated (MI, sudden death, HF death)	40
CBIS and CBIS II trials	Bisoprolol (10 mg/day)	Significant reduction in hospitalization, all-cause mortality by 34%	35
MDC	Metoprolol	Improved quality of life, LVEF, no significant change in mortality	32
MERIT-HF	Metoprolol (200 mg/day)	Significant reduction in hospitalization, all-cause mortality by 34%	33
US Carvedilol	Carvedilol (6.25-25 mg every 12 hours)	Significant reduction in hospitalization, all-cause mortality by 35%	34
COPERNICUS	Carvedilol (25 mg every 12 hours)	Significant reduction in mortality by 35%	36
CAPRICORN	Carvedilol (25 mg every 12 hours)	Significant reduction in mortality by 23%	37

MDC, Metoprolol in Dilated Cardiomyopathy; *MERIT-HF*, Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; *CBIS*, Cardiac Insufficiency Bisoprolol Study; *CBIS II*, Cardiac Insufficiency Bisoprolol Study II; *BEST*, Beta-blocker Evaluation of Survival.

system, improve the morbidity and mortality of patients with HF.[28,29] Data from more than 20 placebo-controlled clinical trials (Table 4) involving about 20,000 patients with HF (MDC, MERIT-HF, RESOLVED, COPERNICUS, MOCHA, PRECISE, CIBIS, and CIBIS II) and meta-analysis have shown that use of β-blockers in patients with stable NYHA class II to IV HF significantly reduces morbidity (4 fewer hospitalization per 100 patients treated) and in some trials even mortality (3.8 lives saved per 100 patients who received β-blocker). There is no convincing evidence that use of β-blockers has any beneficial effect on patients with class I NYHA HF, but it should be used in patients with class I NYHA HF with comorbid conditions such as patients with myocardial infarction and/or chronic USA. Both selective (bisoprolol, sustained-release metoprolol succinate) and nonselective (carvedilol) β-blockers were effective in reducing morbidity and mortality in HF patients, at least in part by improving left ventricular ejection fraction up to 10%, exercise capacity, and cardiac remodeling, and by reducing the incidence of AF.[30-34]

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial evaluated the effectiveness of bisoprolol in 2647 patients with symptomatic NYHA class III or IV HF with ejection fraction (EF) ≤35%. The trial was terminated early because of significant reduction in mortality rate (32% less) in bisoprolol group. There was also 25% fewer deaths from cardiovascular cause and a 39% reduction in sudden death in bisoprolol group.[35] Similar results were obtained in The United States Carvedilol Heart Failure Study Group, The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN), and The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) trials.[36,37]

The beneficial effect of β-blockers in HF patients may not be a result of its class. β-blockers with sympathomimetic activity (acebutolol, pindolol) or with class III antiarrhythmic activity (sotalol) should not be used in HF patients because of an increase in morbidity and mortality.[38-40] In a randomized, double-blind, placebo-controlled trial involving 2708 patients with NYHA class III (92% of patients) and class IV (8% of patients) with EF 35% or less, bucindolol did not show any survival benefit.[41] Currently the American College of Cardiology/American Heart Association guidelines recommend only one of the three β-blockers (bisoprolol, carvedilol, and metoprolol succinate) for patients with stable chronic systolic HF. Fluid retention may need to be minimized before starting β-blockers by increasing diuretic dose. These recommendations also apply to all patient populations, even those who were under-represented in those clinical trials.[42]

The difference in the beneficial effects of β-blockers in HF with left ventricular dysfunction patients should be interpreted with caution and should be based on the large clinical trials. In small clinical trials performed so far, some β-blockers have shown promising results in the treatment of HF patients; therefore, in the absence of larger clinical trials, only those β-blockers with evidence-based data (e.g., carvedilol, metoprolol, and bisoporolol) should be considered for use in patients with HF.[43,44] During HF exacerbation and decompensation, β-blockers should not be discontinued unless the patient manifests signs and symptoms of severe systemic hypoperfusion. In such patients, the β-blocker should be discontinued but restarted once the patient is hemodynamically stable. Decompensated HF patients who are not on a β-blocker should be stabilized first and the β-blocker started when patients are discharged (Table 5).

β-blockers in stable angina and acute coronary syndrome

The 2002 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines updated in 2007

Table 5 Recommended β-blocker doses for HF patients with systolic dysfunction

β-blocker	Initial starting dose	Dosing frequency per day	Target daily dose	Ref
Bisoprolol	1.25 mg	1	10 mg/day	35
Carvedilol	3.125 mg	2	50-100 mg/day	34,36,37
Metoprolol succinate CR/XL	12.5 or 25 mg	1	200 mg/day	32,33

and the European Society of Cardiology, recommend β-blockers as an initial therapy for all stable angina patients with or without MI unless contraindicated. When β-blockers are contraindicated, long-acting CCBs or long-acting nitrates are recommended.[45] Propranolol use in stable angina patients was able to improve exercise tolerance, reduce anginal chest pain by 50%, and decrease sublingual nitroglycerin use in 84% of the patients (n = 63).[46] β-blockers in these patients are recommended indefinitely and using an appropriate dose is important. In one study, all doses of atenolol (25, 50, 100, and 200 mg/day) significantly improved angina symptoms and the need for nitroglycerin, but only 100 and 200 mg/day of atenolol was able to increase exercise capacity compared with placebo.[47]

Although beneficial outcomes of β-blockers in angina are thought to be a class effect, the ACC/AHA guidelines state that β-blockers without ISA are preferred in patients with USA or non–ST-segment elevation/non–Q wave myocardial infarction. The therapeutic goal of β-blocker use is to reduce anginal symptoms and improve exercise tolerance, minimizing adverse effects with a target resting heart rate in the range of 55–60 beats/min as recommended by 2002 ACC/AHA guidelines and guidelines focused update in 2007.[43]

β-blocker use in patients with a history of AMI or HF improves mortality. There are no convincing data that support a decrease in mortality from β-blocker use in patients with stable angina without MI or HF. β-blockers have not been shown in any clinical trial to decrease the incidence of MI. However, it has been demonstrated to reduce the morbidity and mortality if given after AMI.[48] Multiple trials and meta-analysis have supported the beneficial effects of β-blockers on morbidity and mortality after an ST elevation– or non-ST–elevation AMI. Moreover, timely use of β-blocker has also shown to reduce the size of infarct.[49]

Results from a randomized, placebo-controlled trial (COMMIT/CCS2 trial) of about 45,000 subjects indicated that early use of β-blockers in patients with an AMI reduces the risk of re-infarction and ventricular fibrillation, but may increase the risk of cardiogenic shock. Therefore, authors of the article recommend using β-blockers in AMI only after patients are hemodynamically stable.[50,51]

Results from the TIMI-IIB trial supports that early metoprolol administration significantly reduces recurrent chest pain, re-infarction, or death within the first 21 days after an AMI. ACC/AHA recommends starting a β-blocker in all patients within 24 hours of AMI, unless contraindicated.[52-54]

β-blockers and AF

Atrial fibrillation (AF) is a common cardiac arrhythmia and is a frequent complication in HF patients. Results from the COMET trial suggested that AF in HF patients increases the risk of death and number of hospitalizations.[55] New-onset AF in HF patients who were already on a β-blocker was also associated with increased mortality.[55] Several clinical trials have shown that β-blockers like metoprolol or carvedilol alone or in combination with other medications such as digoxin or CCB have favorable outcome on morbidity and mortality from AF.[56-58] Therapeutic effect of β-blockers in AF is mainly a result of ventricular rate control and may be a class effect.[59] In the AFFIRM trial, β-blocker alone was as effective as digoxin or CCB plus digoxin, but was superior to CCB alone in its efficacy to control heart rate at rest and during exertion.[59]

Perioperative use of β-blockers

Because AF is one of the common complications in postoperative surgery, especially after heart surgery such as coronary artery bypass grafting (CABG), a β-blocker is frequently used preoperatively to prevent the incidence of AF. Although all β-blockers are effective, results from the COMPACT study showed that carvedilol was better than metoprolol in the prevention of postoperative AF in patients after CABG.[60]

In general, clinical trials investigating the use of β-blockers (metoprolol, atenolol, bisoprolol) in the noncardiac perioperative period have yielded conflicting results. In a randomized, controlled trial conducted in 190 hospitals and 23 countries (POISE trial), metoprolol (100 mg) given 2 to 4 hours before noncardiac surgery, and 200 mg a day thereafter for 30 days, produced mixed results. At 30 days, death from cardiovascular events, nonfatal myocardial infarction, or nonfatal cardiac arrest (primary endpoint) decreased from 6.9% in the placebo group to 5.8% in the metoprolol group (95% CI 0.70-0.99, $P < 0.0399$). Incident of myocardial infarction was decreased from 5.7% (placebo) to 4.2% (metoprolol) (95% CI 0.60-0.89, $P < 0.0017$). Total mortality and incident of stroke, however, were increased significantly in metoprolol groups.[61] Similar results were obtained from other systematic reviews and meta-analysis of 22 trials.

Careful patient selection and close monitoring (blood pressure and heart rate) are important factors that could determine the effectiveness of β-blockers when used perioperatively.[62] In November 2009, the American College of Cardiology Foundation (ACCF) and AHA released a report entitled "Focused Update to the Practice Guideline from 2007."[63] Some of the recommendations from this updates are (1) patients who are already on a β-blocker for ACCF/AHA Class I indications should continue taking it (Level of Evidence [LOE]: C); (2) β-blockers are recommended for patients undergoing vascular surgery but are at high cardiac risk because of CAD from their history or based on stress testing (LOE: B); (3) A β-blocker is reasonable in patients who undergo vascular surgery and are identified to have high cardiac risk such as history of ischemic heart disease; history of compensated or previous HF; history of cerebrovascular disease, diabetes mellitus, and renal insufficiency (serum creatinine >2 mg/dL) (LOE: C); (4) it is reasonable to use β-blockers in patients who are undergoing intermediate-risk surgery and are at high cardiac risk (presence of more than one clinical risk factors) or have CAD (LOE: B). In patients who are undergoing intermediate-risk surgery or vascular surgery, do not have CAD but have one clinical risk factor, usefulness of the β-blocker is uncertain (LOE: C). The value of β-blockers is uncertain in patients undergoing vascular surgery and who have no clinical risk factor for cardiac complications and are not already on a β-blocker (LOE: B). High-dose blocker without titration may be harmful to patients who were not taking a β-blocker previously and are undergoing noncardiac surgery (LOE: B).[63]

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