

## Therapeutic Class Overview

### Beta-adrenergic Blocking Agents

#### INTRODUCTION

- Approximately 121.5 million American adults have at least 1 type of cardiovascular (CV) disease according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. The age-adjusted prevalence of all types of heart disease was 10.6% in 2017. CV disease deaths were most often caused by coronary heart disease (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (HF; 9.4%), and other causes (17.6%) (*Virani et al 2020*).
- Beta-adrenergic blocking agents (beta-blockers) are a group of drugs that block the sympathomimetic effects of catecholamines on beta receptors. This results in negative inotropic and chronotropic effects and relaxation of smooth muscle.
- Beta-blockers have varied pharmacologic properties.
  - Cardioselective beta-blockers preferentially interact with beta<sub>1</sub>-receptors, which are predominantly found in the heart. Non-cardioselective beta-blockers also interact with beta<sub>2</sub>-receptors found on smooth muscle in the lungs, blood vessels, and other tissues. The cardioselectivity of beta-blockers is dose-dependent; therefore, beta<sub>2</sub> blockade can occur at higher doses with certain cardioselective agents.
  - Some beta-blockers (acebutolol and pindolol) have intrinsic sympathomimetic activity (ISA), which may result in a lower incidence of bradycardia and bronchoconstriction (*Facts and Comparisons 2020*). In addition, some beta-blockers (nebivolol and propranolol) have higher lipophilicity, which may increase the risk for central nervous system-related adverse events (*Facts and Comparisons 2020*).
  - Carvedilol and labetalol also block alpha-adrenergic receptors and may reduce peripheral resistance more than other beta-blockers (*Clinical Pharmacology 2020*).
- Specific indications for the beta-blockers vary by product. Most beta-blockers (all except sotalol) are approved to treat hypertension (HTN). The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP)  $\geq$  130/80 mm Hg (*Whelton et al 2017*). Nearly half of American adults (46%) have HTN based on this definition. Other indications for 1 or more beta-blockers include, but are not limited to: angina pectoris, arrhythmias, myocardial infarction (MI), HF, left ventricular dysfunction following MI, treatment of essential tremor, and migraine prophylaxis.
- Most of the beta-blockers are available generically. There are no generics available for Bystolic (nebivolol) and branded Levatol (penbutolol), which was discontinued in 2014. Brand Hemangeol is an oral solution of propranolol in a strength of 4.28 mg/mL (equivalent to 3.75 mg); however generic oral solutions of propranolol are available in strengths of 4 and 8 mg/mL.
- There has been extensive experience with beta-blockers in clinical practice, and clinical trials do not consistently demonstrate a clinical advantage of one agent over another for most Food and Drug Administration (FDA)-approved indications. In general, treatment guidelines do not recommend the use of one beta-blocker over the other, as recommendations regarding the use of these agents are made for the class as a whole. There are some exceptions, however. Guidelines do recognize the role of 3 beta-blockers (carvedilol, bisoprolol, and extended release metoprolol) for the reduction of mortality and hospitalization in patients with HF (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017*). Also, sotalol has some unique properties and is considered separately from the other beta-blockers, as this agent is not indicated to treat HTN and is instead used to treat certain ventricular arrhythmias or for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter.
- Although some single-ingredient beta-blockers have several indications, the beta-blocker/diuretic combination products are FDA-approved only for the treatment of HTN. Patients with HTN frequently require the use of 2 or more agents from different therapeutic classes in order to adequately reduce BP, and the dose of each product should be titrated to its desired effect. Thus, the place in therapy for the beta-blocker/diuretic combinations is for patients who require both agents at doses for which a combination product is available. Several of the combination products (all except for Dutoprol and Ziac) contain specific wording in their prescribing information stating that the product is not approved for initial therapy (*Gradman 2012*).
- Both beta-blockers and diuretics are well established in the management of HTN. The choice of antihypertensive agent(s) for a particular patient will depend on the patient's comorbidities.

- All of the beta-blockers contained within the combination products are also available generically as single-entity agents. The diuretics hydrochlorothiazide (HCTZ) and chlorthalidone are available generically as single-entity agents. All of the combination products except for Dutoprol (metoprolol succinate extended release/HCTZ) are available generically. Dutoprol is not available as a generic but its individual components are.
- Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence to therapy (*Mancia et al 2013*).
- This class includes the orally-administered beta-blockers, as well as the orally-administered alpha/beta-blocking agents, carvedilol and labetalol, and the beta-blocker/diuretic combination products. Several beta-blockers are also available in intravenous (IV) forms for in-hospital use; however, the IV formulations are not included within the scope of this review.
- Medispan drug class: Beta Blockers - Beta Blockers Non-Selective; Beta Blockers Cardio-Selective; Alpha-Beta Blockers; Antihypertensive Combinations - Beta Blocker & Diuretic Combinations

**Table 1. Medications Included Within Class Review**

Drug	Generic Availability
<b>Single-Entity Beta-blockers</b>	
acebutolol*	✓
Betapace, Betapace AF, Sorine, Sotylize (sotalol)	✓
betaxolol*	✓
bisoprolol*	✓
Bystolic (nebivolol)	-
Coreg, Coreg CR (carvedilol)	✓
Corgard (nadolol)	✓
Hemangeol, Inderal LA, Inderal XL, Innopran XL (propranolol)*	✓ ‡
Toprol XL, Kaspargo Sprinkle (metoprolol succinate extended release)	✓ †
labetalol*	✓
Lopressor (metoprolol tartrate)	✓
pindolol*	✓
Tenormin (atenolol)	✓
timolol*	✓
<b>Beta-blocker/Diuretic Combinations</b>	
Dutoprol (metoprolol succinate extended release/HCTZ)	-
Lopressor HCT (metoprolol tartrate/HCTZ)	✓
propranolol/HCTZ*	✓
Tenoretic (atenolol/chlorthalidone)	✓
Ziac (bisoprolol/HCTZ)	✓

‡ Hemangeol (propranolol oral solution), Inderal XL, and Innopran XL are brand-name only.

† Kaspargo Sprinkle (metoprolol succinate extended release capsule) is brand name only.

|| Sotylize (sotalol oral solution) is brand-name only.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

**INDICATIONS**

**Table 2. Food and Drug Administration Approved Indications for Single-Entity Beta-blockers**

Generic Name	Hypertension	Angina pectoris	Cardiac arrhythmias*	Myocardial infarction	Heart failure	Pheochromocytoma	Migraine prophylaxis	Hypertrophic subaortic stenosis	Proliferating infantile hemangioma requiring systemic therapy	Essential tremor	Left ventricular dysfunction following myocardial infarction
acebutolol	✓ †		✓								
atenolol	✓ †	✓ ‡		✓ §							
betaxolol	✓ †										
bisoprolol	✓										
carvedilol	✓ ¶¶				✓ #						✓ **
labetalol	✓ ††										
metoprolol	✓ §§	✓		✓ ¶¶	✓ ##						
nadolol	✓ †	✓ ***									
nebivolol	✓										
pindolol	✓ †										
propranolol	✓ †.†††	✓ †††	✓	✓ §§§		✓	✓	✓ ¶¶¶	✓ ††††	✓ ###	
sotalol			✓								
timolol	✓ †			✓ ****			✓				

\* See Table 3 for the specific cardiac arrhythmias for which these agents are indicated.  
 † May be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.  
 ‡ Indicated for the long term management of patients with angina pectoris due to coronary atherosclerosis.  
 § Indicated for the management of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality.  
 || May be used alone or in combination with other antihypertensive agents.  
 ¶¶ Indicated for the management of essential HTN.  
 # Indicated for the treatment of mild to severe chronic HF of ischemic or cardiomyopathic origin, usually in addition to diuretics, angiotensin converting enzyme inhibitors and digitalis to increase survival, and also to reduce the risk of hospitalization.  
 \*\* Indicated to reduce CV mortality in clinically stable patients who survived the acute phase of an MI and have a left ventricular ejection fraction ≤ 40% (with or without symptomatic HF).  
 †† Labetalol tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.  
 §§ Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets may be used alone or in combination with other antihypertensive agents.  
 ||| Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets are indicated in the long term treatment of angina pectoris.  
 ¶¶¶ Metoprolol tartrate tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality when used alone or in conjunction with IV metoprolol tartrate. Oral therapy can be initiated after IV therapy or, alternatively, oral treatment can begin within 3 to 10 days of the acute event.  
 ## Metoprolol succinate extended release tablets are indicated for the treatment of stable, symptomatic (New York Heart Association Class II or III) HF of ischemic, hypertensive or cardiomyopathic origin. Metoprolol succinate extended release capsules are indicated for the treatment of patients with HF to reduce the risk of CV mortality and HF-related hospitalization.  
 \*\*\* Indicated for the long term management of patients with angina pectoris.  
 ††† Inderal XL and Innopran XL are indicated for the treatment of HTN only.  
 †††† Indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris due to coronary atherosclerosis.  
 §§§ Propranolol tablets and oral solution are indicated to reduce CV mortality in patients who have survived the acute phase of an MI and are clinically stable.  
 |||| Propranolol tablets and oral solution are indicated as an adjunct to alpha-adrenergic blockade to control BP and reduce symptoms of catecholamine-secreting tumors.  
 ¶¶¶¶ Improves New York Heart Association functional class in symptomatic patients with hypertrophic subaortic stenosis.  
 ### Propranolol tablets and oral solution are indicated for the management of familial or hereditary essential tremor.  
 \*\*\*\* Indicated in patients who have survived the acute phase of an MI, and are clinically stable, to reduce CV mortality and the risk of reinfarction.

††† Only approved for Hemangeol oral solution. Hemangeol is not FDA-approved for any other indication.

(Prescribing information: acebutolol 2017, betaxolol 2020, bisoprolol 2019, Betapace and Betapace AF 2018, Bystolic 2019, Coreg 2017, Coreg CR 2020, Corgard 2019, Hemangeol 2020, Inderal LA 2019, Inderal XL 2017, Innopran XL 2017, Kapsargo 2018, labetalol 2019, Lopressor 2017, pindolol 2017, propranolol solution 2017, propranolol tablets 2019, Sorine 2020, Sotylize 2015, Tenormin 2017, timolol 2018, Toprol XL 2019)

**Table 3. FDA-Approved Cardiac Arrhythmia Indications**

Indication	acebutolol	propranolol	sotalol
Control ventricular rate in patients with atrial fibrillation and a rapid ventricular response		✓ (oral solution, tablet)	
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AFIB/AFL] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm)			✓
Management of ventricular premature beats	✓		
Treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia**			✓

\* Limitations of use: Because sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol.

\*\* Limitations of use: Sotalol may not enhance survival in patients with ventricular arrhythmias. Because of the proarrhythmic effects of Betapace/Betapace AF, including a 1.5 to 2% rate of Torsade de Pointes (TdP) or new ventricular tachycardia/fibrillation (VT/VF) in patients with either non-sustained ventricular tachycardia (NSVT) or supraventricular arrhythmias (SVT), its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Avoid treatment of patients with asymptomatic ventricular premature contractions.

(Prescribing information: acebutolol 2017, propranolol solution 2017, propranolol tablets 2019, Betapace and Betapace AF 2018, Sorine 2020, Sotylize 2015)

**Table 4. FDA-Approved Indications for Beta-blocker/Diuretic Combinations**

Drug	HTN
Dutoprol (metoprolol succinate extended release/HCTZ)	✓
Lopressor HCT (metoprolol tartrate/HCTZ)	✓ *
propranolol/HCTZ	✓ *
Tenoretic (atenolol/chlorthalidone)	✓ *
Ziac (bisoprolol/HCTZ)	✓

\*The fixed-dose combination product is not indicated for initial therapy of HTN. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

(Prescribing information: Dutoprol 2020, Lopressor HCT 2012, propranolol and HCTZ 2020, Tenoretic 2018, Ziac 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

### CLINICAL EFFICACY SUMMARY

- Clinical trials demonstrating the safety and efficacy of beta-blockers for their FDA-approved indications have demonstrated that beta-blockers are superior to placebo and efficacious compared to active comparators for these varied indications, including:
  - HTN (Dahlöf et al 1991, Davidov et al 1988, Dhakam et al 2008, Dietz et al 2008, Fogari et al 1997, Giles et al 2014, Greathouse 2010, Materson et al 1990, Neutel et al 2010, Stoschitzky et al 2006, Van Bortel et al 2005, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1977, Wald et al 2008)
  - Angina (Pandhi et al 1985, van der Does et al 1999, Weiss et al 1998)
  - Arrhythmia (Lui et al 1983, Seidl et al 1998)
  - Heart failure (Bristow et al 1996, CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, Dargie et al 2001, Di Lenarda et al 1999, Flather et al 2005, Goldstein et al 2001, Krum et al 1995, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Waagstein et al 1993)

Data as of November 23, 2020 RR-U/MG-U/LMR

Page 4 of 19

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- Infantile hemangiomas (*Bauman et al 2014, Novoa et al 2018*)
- Essential tremor (*Calzetti et al 1981, Gironell et al 1999, Yetimalar et al 2005*)
- Migraine prophylaxis (*Ashtari et al 2008, Domingues et al 2009, Jackson et al 2019, Rao et al 2000, Schellenberg et al 2008, Tfelt-Hansen et al 1984*)
- Head-to-head trials have demonstrated that no one beta-blocker is consistently superior compared to the others for the treatment of HTN (*Czuriga et al 2003, Davidov et al 1988, Dhakam et al 2008, Fogari et al 1997*).
- Trials have demonstrated CV advantages with beta-blocker use in patients with prior MI; however, recent post-hoc analyses examining the use of beta-blockers have been mixed (*Bangalore et al 2014, Dahl Aarvik et al 2019, Freemantle et al 1999, Gottlieb et al 2001, Jonsson et al 2005, Olsson et al 1992*).
- For the treatment of HF, a survival benefit has been demonstrated with bisoprolol, carvedilol, and sustained release metoprolol succinate; however, only carvedilol and metoprolol succinate extended release are FDA-approved for the treatment of HF. Carvedilol has demonstrated superiority to other beta-blockers in certain populations. Beta-blockers that have been shown to reduce mortality in patients with systolic dysfunction include carvedilol, bisoprolol, and long-acting metoprolol (*Bristow et al 1996, CIBIS-II Investigators and Committees 1999, Dargie 2001, Di Lenarda et al 1999, Goldstein et al 2001, Hamaad et al 2007, Maack et al 2001, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Sanderson et al 1999*). In elderly patients with HF, nebivolol demonstrated a significant improvement in a composite measure of death or CV hospitalization; however, differences for the individual components of the composite measure did not reach statistical significance (*Flather et al 2005*).
  - Head-to-head trials have compared metoprolol to carvedilol in patients with HF; however, available trials used the immediate release formulation of metoprolol rather than the extended release formulation that has FDA approval for this indication (*Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Poole-Wilson et al 2003, Sanderson et al 1999*). Most of the comparative trials have been small and have evaluated outcomes other than mortality (*Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Sanderson et al 1999*). One larger trial, COMET (N = 3029), demonstrated that all-cause mortality was significantly lower in patients treated with carvedilol compared to patients treated with metoprolol tartrate (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.74 to 0.93; p = 0.0017). However, questions have been raised about the choice of metoprolol formulation and its dosing for this trial, so definitive conclusions could not be made (*Kveiborg et al 2007*).
  - A meta-analysis (MA) that included trials that evaluated immediate and sustained release metoprolol revealed that treatment with carvedilol improved mean left ventricular ejection fraction significantly more than treatment with metoprolol (*Packer et al 2001[a]*).
  - Another MA found that carvedilol significantly reduced the incidence of post-operative atrial fibrillation when compared to metoprolol in patients following a coronary artery bypass grafting (CABG) procedure (*DiNicolantonio et al 2014*).
  - Several meta-analyses have confirmed the mortality benefit of beta-blockers for the treatment of HF (*Brophy et al 2001, Chatterjee et al 2013, Lechat et al 1998, Whorlow et al 2000*).
- For the treatment of infantile hemangiomas, a systematic review (SR) and MA of 28 trials concluded that oral propranolol probably improves clinician-assessed clearance vs placebo (risk ratio, 16.61; 95% CI, 4.22 to 65.34) and provides a clinician-assessed reduction in mean hemangioma volume by 45.9% (95% CI, 11.60 to 80.20) (*Novoa et al 2018*). Compared with topical timolol, oral propranolol was not significantly different in the proportion of patients with clinician-assessed reductions of 50% or greater in hemangioma size. Another SR of 9 trials supports the efficacy of oral atenolol for the treatment of infantile hemangioma based on a response rate of 0.90 (95% CI, 0.85 to 0.93) and an overall rate of adverse events of 0.26 (95% CI, 0.12 to 0.47) (*Wang et al 2018*).

### Combination products

- Most trials compared the combination product to placebo or to 1 or both of the individual product components. Results demonstrate that:
  - The combination products are superior to placebo (*de Leeuw et al 1997, Lewin et al 1993, Nissinen et al 1980*).
  - Additional BP lowering is achieved when the combination therapy is compared to 1 or both of the individual drug components administered as monotherapy (*Dafgard et al 1981, Fogari et al 1984, Frishman et al 1994, Frishman et al 1995, Hansson et al 1999, Leonetti et al 1986, Liedholm et al 1981, Smilde et al 1983, Stevens et al 1982*).
  - The CAPPP study compared an angiotensin converting enzyme (ACE) inhibitor to treatment with a diuretic and/or beta-blockers. For both diabetic and non-diabetic patients, both regimens were equally effective in preventing the composite of fatal and non-fatal MI, stroke, and CV deaths (*Hansson et al 1999*). A sub-analysis of diabetic patients



within the CAPPP trial found that in hypertensive diabetic patients, captopril (ACE inhibitor) was superior to a diuretic and/or beta-blocker antihypertensive treatment regimen in preventing CV events, especially in those with metabolic decompensation (*Niskanen et al 2001*). Further studies should be performed to validate beta-blockers in combination with a diuretic and their place in therapy with diabetic patients.

**CLINICAL GUIDELINES**

- Hypertension:
  - The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults (*Whelton et al 2017*) offers updated classifications of HTN and goals of treatment (see Table 5).

**Table 5. Classification of BP measurements**

BP Category	BP	Treatment or follow-up
Normal	SBP < 120 mm Hg and DBP < 80 mm Hg	<ul style="list-style-type: none"> <li>▪ Evaluate yearly; lifestyle changes are recommended</li> </ul>
Elevated	SBP 120 - 129 mm Hg and DBP < 80 mm Hg	<ul style="list-style-type: none"> <li>▪ Evaluate in 3 to 6 months; lifestyle changes are recommended</li> </ul>
HTN stage 1	SBP 130 - 139 mm Hg or DBP 80 - 89 mm Hg	<ul style="list-style-type: none"> <li>▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator.</li> <li>▪ If ASCVD risk is &lt; 10%, lifestyle changes are recommended. A BP target of &lt; 130/80 mm Hg may be reasonable.</li> <li>▪ If ASCVD risk is &gt; 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of &lt; 130/80 mm Hg is recommended.</li> </ul>
HTN stage 2	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	<ul style="list-style-type: none"> <li>▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.</li> </ul>

Abbrev: ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, CKD = chronic kidney disease, CVD = cardiovascular disease, DBP= diastolic blood pressure, DM = diabetes mellitus, SBP = systolic blood pressure

- In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
  - First-line antihypertensive agents include: thiazide diuretics, calcium channel blockers (CCBs), and ACE inhibitors or angiotensin II receptor blockers (ARBs).
  - Diuretics, ACE inhibitors, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
    - Beta-blockers are not recommended as first-line agents unless the patient has ischemic heart disease (IHD) or HF.
    - Cardioselective beta-blockers (atenolol, betaxolol, bisoprolol, metoprolol tartrate and succinate) are preferred in patients with bronchospastic airway disease requiring a beta-blocker.
    - Non-cardioselective beta-blockers (ie, nadolol, propranolol) should be avoided in patients with reactive airways disease.
    - Bisoprolol, carvedilol, and metoprolol succinate are preferred in patients with HF with reduced ejection fraction (HFrEF).
    - In general, beta-blockers with ISA (ie, acebutolol, carteolol, penbutolol, pindolol) should be avoided, especially in patients with IHD or HF.
- Most HTN guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a CCB as first line therapy (*Go et al 2014, James et al 2014, Mancina et al 2013, Weber et al 2014, Whelton et al 2017, Williams et al 2018*).

- In the treatment of severe HTN in pregnancy, labetalol is outlined as an option with consideration of maternal and fetal side effects (*American Diabetes Association 2020, Bushnell et al 2014, de Boer et al 2017, Weber et al 2014*).
- Beta-blockers have strong clinical outcome benefits in hypertensive patients with a history of MI, HF, acute coronary syndrome, and in the management of angina pectoris. Some guidelines endorse beta-blockers for first-line therapy in these populations (*Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014, Williams et al 2018*).
- Patients with resistant HTN (defined as above-goal elevated BP despite concurrent use of 3 drug classes) may require additional treatment (*Carey et al 2018*). Guidelines from the AHA/ACC for the treatment of resistant HTN suggest beta-blockers may be helpful in patients with obstructive sleep apnea, coarctation of the aorta, and patients without bradycardia who have failed multiple other antihypertensives. No specific beta-blocker is preferred by this guideline.
- The beta-blockers are also a mainstay of HF treatment, as evidenced by recommendations within treatment guidelines (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2017*). Of note, carvedilol and metoprolol succinate extended release are the only 2 beta-blockers that are FDA-approved for the treatment of HF, but a mortality benefit has also been shown for bisoprolol in clinical trials, and all 3 are recognized as appropriate options in clinical guidelines (*CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, MERIT-HF Study Group 1999, Ponikowski et al 2016, Waagstein et al 1993, Yancy et al 2013, Yancy et al 2017*).
  - Conclusive data on the medical management of HF in patients with a systemic right ventricle (RV) are lacking, despite the high incidence of late clinical HF and sudden death in this population. Use of conventional HF medications may be problematic because of preexisting sinus node dysfunction, heart block, baffle stenosis, nondistensible atria, and restrictive RV physiology. Beta-blockade may exacerbate bradyarrhythmias, whereas vasodilation could be counterproductive in patients with nondistensible atria or restrictive physiology (*Stout et al 2016*).
- Guidelines also support the use of beta-blockers for additional CV diseases including stable ischemic heart disease, unstable angina, MI (acute and long-term after MI), rate control in atrial fibrillation and atrial flutter, maintenance of normal sinus rhythm in atrial fibrillation (sotalol), non-ST-segment elevation acute coronary syndromes, select ventricular and supraventricular arrhythmias, complications following CABG, valvular heart disease, and hypertrophic cardiomyopathy (*Amsterdam et al 2014[a,b], Brugada et al 2019, Fihn et al 2012, Fihn et al 2014, Gersh et al 2011, Ibanez et al 2018, January et al 2014[a,b], January et al 2019, Jneid et al 2012, Knuuti et al 2019, Montalescot et al 2013, Neumann et al 2018, Nishimura et al 2014[a,b], Nishimura et al 2017, O'Gara et al 2013, Page et al 2016, Priori et al 2015, Roffi et al 2016, Rosendorff et al 2015*).
- Metoprolol, propranolol, and timolol are established as effective for migraine prevention (*Silberstein et al 2012, Snow et al 2002, American Headache Society 2019, Oskoui 2019*).
- Propranolol is the only beta-blocker that is FDA-approved for the treatment of essential tremor. Guidelines recommend propranolol, long-acting propranolol, or primidone for limb tremor in essential tremor, depending on concurrent medical conditions and potential side effects (*Zesiewicz et al 2011*).
- A 2019 treatment guideline on infantile hemangioma was published by the American Academy of Pediatrics. If pharmacologic therapy is needed, oral propranolol should be used as a first-line agent. No other systemic beta-blockers are recommended due to a lack of high-quality data (*Krowchuk et al 2019*).

## SAFETY SUMMARY

- Beta-blockers have a number of contraindications related to their pharmacologic properties. They should be avoided in patients with sinus bradycardia and second- or third-degree heart block. They also should not be initiated in patients with uncontrolled HF or cardiogenic shock. Based on their ability to block beta<sub>2</sub> receptors in the lung, beta-blockers should generally not be used (or used with caution) in patients with asthma and/or chronic obstructive pulmonary disease. This is particularly a concern with non-selective beta-blockers. Other contraindications vary based on the specific drug and the clinical use.
- A boxed warning exists for atenolol, metoprolol (non-boxed warning for metoprolol succinate extended release capsules), nadolol, propranolol extended release capsules, and timolol: worsening angina, MI, and arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with beta-blockers. When discontinuing a chronically administered beta-blocker, particularly in patients with IHD, the dosage should be gradually reduced over a period of 1 to 2 weeks, and the patient should be carefully monitored. Sotalol also carries a boxed warning, noting that patients initiated or reinitiated on sotalol or sotalol AF should be placed for a minimum of 3 days (on

their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Creatinine clearance (CrCL) should be calculated prior to dosing.

- Hemangeol has specific contraindications for use in premature infants with corrected age < 5 weeks, infants weighing < 2 kg, BP < 50/30 mm Hg, and pheochromocytoma.
- Key additional warnings and precautions include:
  - Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in peripheral vascular disease.
  - Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge when taking a beta-blocker. Such patients may also be unresponsive to the usual doses of epinephrine used to treat allergic reactions.
  - Beta-blocker therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
  - Some beta-blockers may potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
  - Beta-blockers should not be given to patients with untreated pheochromocytoma. In patients with this condition, a beta-blocker should be given only after an alpha-blocker has been initiated.
  - Bradycardia and/or hypotension may occur.
  - Sotalol can provoke new or worsened ventricular arrhythmias in some patients. This may include Torsades de Pointes, the risk of which increases with increasing prolongation of the QT interval. Use with particular caution if the QTc is > 500 milliseconds. Use is contraindicated in patients with congenital or acquired long QT syndrome or if serum potassium < 4 mEq/L.
  - The value of using betaxolol in psoriatic patients should be carefully weighed since it has been reported to cause an aggravation in psoriasis.
  - Hemangeol has demonstrated an increased risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Infants with large facial infantile hemangioma should be investigated for potential arteriopathy associated with PHACE syndrome prior to therapy.
- Common adverse reactions (occurring in > 10% of patients for at least 1 medication) include: bradycardia, chest pain, hypotension, palpitations, dizziness, drowsiness, fatigue, headache, insomnia, lightheadedness, hyperglycemia, diarrhea, nausea, weight gain, decreased sexual ability, weakness, and dyspnea.

### Combination products

- Based on the beta-blocker component, the beta-blocker/diuretic combinations are contraindicated in patients with sinus bradycardia, second- or third-degree heart block, cardiogenic shock, and overt cardiac failure.
- Based on the diuretic component, the beta-blocker/diuretic combinations are contraindicated in patients with anuria, hypersensitivity to the ingredients, or hypersensitivity to sulfonamide-derived drugs.
  - Lopressor HCT and Dutoprol are contraindicated in patients with sick sinus syndrome, which includes patients with sinus bradycardia and patients with sinus pauses or arrest.
  - Lopressor HCT is contraindicated in those with severe peripheral arterial circulatory disorders.
  - Propranolol/HCTZ is contraindicated in patients with bronchial asthma.
- A precaution is included in some package inserts (Lopressor HCT and Ziac) related to the diuretic component of HCTZ-containing products regarding the risk for non-melanoma skin cancer. Patients taking HCTZ should protect skin from the sun and undergo regular skin cancer screening.
- Boxed warning for Dutoprol, Lopressor HCT, and propranolol/HCTZ: Do not discontinue abruptly; withdraw gradually with appropriate monitoring to avoid potential exacerbation of IHD. This is also a warning for Tenoretic and Ziac (although not boxed).
- Avoid in overt HF; use with caution in patients with controlled HF.
- Avoid in patients with bronchospastic disease. Low doses of beta<sub>1</sub> selective agents may be used in patients with bronchospastic disease when no acceptable alternative exists.
- Dutoprol has a warning for bradycardia, particularly in patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders. Concomitant use of beta adrenergic blockers, non-dihydropyridine CCB, digoxin, or clonidine increases the risk. The drug also has additional warnings for increased risk of acute renal failure in patients with chronic kidney disease, severe HF, or volume depletion; and reduced effectiveness of epinephrine when treating anaphylaxis.



- Some beta-blockers may cause hypoglycemia or potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
- Thyrotoxicosis: Beta blockade may mask certain clinical signs of thyrotoxicosis (eg, tachycardia). Abrupt withdrawal of beta blockade may precipitate a thyroid storm.
- Thiazides should be used with caution in severe renal disease, as they may precipitate azotemia in this setting.
- Thiazides should be used with caution in patients with impaired hepatic function because minor alterations of fluid/electrolyte balance may precipitate hepatic coma.
- Adverse reactions reported in > 5% of patients in clinical trials for Dutoprol and Lopressor HCT include bradycardia, dizziness/vertigo, drowsiness/somnolence, fatigue/lethargy, and headache.
- Adverse reaction rates for the other fixed-dose combination products (propranolol/HCTZ, Tenoretic, and Ziac) are not specifically listed in the prescribing information; however, adverse reactions are known based on experience with their components. Notable adverse reactions include HF, intensification of atrioventricular block, bradycardia, peripheral vascular insufficiency, heart rhythm/conduction disturbance, depression, nausea, vomiting, diarrhea, constipation, orthostatic hypotension, dizziness, fatigue, vertigo, headache, hypersensitivity, hyperglycemia, hyperuricemia, and bronchospasm.

## DOSING AND ADMINISTRATION

**Table 6. Dosing and Administration**

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
<b>Single-Entity Beta-blockers</b>				
acebutolol	Capsules	Oral	<u>Cardiac arrhythmias (ventricular)</u> : Twice daily  <u>HTN</u> : Once to twice daily	Dosage adjustment in renal impairment is required.  Older patients have an approximately 2-fold increase in bioavailability and may require lower maintenance doses; avoid doses above 800 mg.
atenolol	Tablets	Oral	<u>Angina pectoris</u> : Once daily  <u>HTN</u> : Once daily  <u>Acute MI*</u> : After initial IV dosing in the acute setting, 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, once or twice daily for a further 6 to 9 days or until discharge.	Dosage adjustment in renal impairment is required.  Atenolol can cause fetal harm when used in pregnancy. Low birth weights have been reported with use; drug is excreted in breast milk; use with caution. Neonates may be at risk for hypoglycemia and bradycardia.
betaxolol	Tablets	Oral	<u>HTN</u> : Once daily	Dosage adjustment in renal impairment is required.  Consideration should be given to reducing the starting dose to 5 mg in elderly patients.
bisoprolol	Tablets	Oral	<u>HTN</u> : Once daily	Dosage adjustment in renal and hepatic impairment is required.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
carvedilol	ER capsules (Coreg CR), tablets (Coreg)	Oral	<p><u>HF</u>: ER capsule: Once daily; Tablet: Twice daily</p> <p><u>HTN</u>: ER capsule: Once daily; Tablet: Twice daily</p> <p><u>Left ventricular dysfunction following MI</u>: ER capsule: Once daily; Tablet: Twice daily</p>	<p>Patients controlled with immediate release (IR) tablets may be switched to ER capsules (see prescribing information for details).</p> <p>When switching from the higher doses of IR carvedilol to ER, a lower starting dose is recommended for the elderly.</p> <p>Contraindicated in severe hepatic dysfunction.</p> <p>ER capsule: Take once daily in the morning with food. Should be swallowed as a whole capsule or may alternatively be opened, and the beads sprinkled over a spoonful of applesauce.</p> <p>Tablet: Take with food.</p>
labetalol	Tablets	Oral	<u>HTN</u> : Twice daily	<p>Dose adjustment is required in the elderly.</p> <p>Use with caution in hepatic dysfunction; metabolism of the drug may be diminished.</p>
metoprolol	ER tablets (succinate; Toprol XL), ER capsules (succinate; Kaspargo), tablets (tartrate)	Oral	<p><u>Angina pectoris</u>: ER tablet or ER capsule: once daily; Tablet: daily in 2 divided doses</p> <p><u>HF</u>: ER tablet (NYHA Class II): once daily [start with 25 mg/day]; ER tablet (severe HF): once daily [start with 12.5 mg/day]; ER capsule: once daily [start with 25 mg/day]</p> <p><u>HTN</u>: ER tablet or ER capsule: once daily; Tablet: daily in single or divided doses</p> <p><u>MI</u>: Tablet: After initial IV dosing in the acute setting, initiate tablets at 50 mg every 6 hours 15 minutes after the last IV dose and continue for 48 hours; thereafter, the maintenance dose is 100 mg twice daily</p>	<p>Hepatic dosage adjustment may be necessary; initiate at low doses with cautious gradual titration.</p> <p>ER tablet or ER capsule: Dosing recommendations are available for pediatric hypertensive patients ≥ 6 years of age; product is not recommended in patients &lt; 6 years.</p> <p>ER tablet: Take with or immediately after meals. ER tablets are scored and can be divided, but not crushed or chewed.</p> <p>ER capsule: swallow whole or sprinkle capsule contents over soft food; mix contents with water for nasogastric tube administration</p> <p>ER capsule: 1 to 1 dose conversion with ER tablet</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Tablet: Take with or immediately after meals. Do not chew.
nadolol	Tablets	Oral	<u>Angina pectoris</u> : Once daily <u>HTN</u> : Once daily	Dosage adjustment in renal impairment is required.
nebivolol	Tablets (Bystolic)	Oral	<u>HTN</u> : Once daily	Dosage adjustment in renal and hepatic impairment is required.
pindolol	Tablets	Oral	<u>HTN</u> : Twice daily	Poor hepatic function may cause blood levels to increase substantially; use with caution.
propranolol	ER capsules (Inderal LA), ER beads capsules (Inderal XL, Innopran XL), oral solution (Hemangeol), oral solution (generic), tablets (generic)	Oral	<u>Angina pectoris</u> : ER capsule (Inderal LA): Once daily; Oral solution, tablet: Daily in 2, 3 or 4 divided doses <u>Cardiac arrhythmias (atrial fibrillation)</u> : Oral solution, tablet: Three to 4 times daily before meals and at bedtime <u>Essential tremor</u> : Oral solution, tablet: Twice daily <u>HTN</u> : ER capsules (all): Once daily; Oral solution, tablet: Twice daily; if control is not adequate, a larger dose, or 3 times daily therapy may achieve better control <u>Hypertrophic subaortic stenosis</u> : Oral solution, tablet: Three to 4 times daily before meals and at bedtime; ER capsule (Inderal LA): Once daily <u>Infantile hemangioma</u> : Oral solution (Hemangeol): Twice daily <u>Migraine prophylaxis</u> : Oral solution, tablet: Daily in divided doses; ER capsule (Inderal LA): Once daily <u>MI</u> : Oral solution, tablet: Twice or 3 times daily <u>Pheochromocytoma</u> : Oral solution, tablet (operable	Propranolol is not indicated for the treatment of hypertensive emergencies.  With propranolol, hepatic insufficiency increases plasma concentration and prolongs the half-life; use with caution.  Hemangeol is not intended for pregnant or nursing women.  Hemangeol should be initiated at ages 5 weeks to 5 months. Administer doses at least 9 hours apart and during or after feeding. Monitor heart rate and BP for 2 hours after first dose or increasing dose. Of 460 infants (aged 5 weeks to 5 months), 60% had complete or near complete resolution of hemangioma at week 24.  Inderal XL and Innopran XL should be administered once daily at bedtime and should be taken consistently either on an empty stomach or with food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			tumors): Daily in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade; Oral solution, tablet (inoperable tumors): Daily in divided doses as adjunct to alpha-adrenergic blockade	
sotalol	Tablets (Betapace, Betapace AF, Sorine), oral solution (Sotylize)	Oral	<p><u>Cardiac arrhythmias (maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter):</u> Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function</p> <p><u>Cardiac arrhythmias (ventricular):</u> Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function</p>	<p>Pediatric dosing is available for the treatment of cardiac arrhythmias (ventricular and symptomatic atrial fibrillation/atrial flutter).</p> <p>Dosage adjustment in renal impairment is required. For treatment of atrial fibrillation or flutter, use is contraindicated if CrCL is &lt; 40 mL/min.</p> <p>See the Betapace or Sorine prescribing information for instructions on compounding an oral solution from the tablets.</p>
timolol	Tablets	Oral	<p><u>HTN:</u> Twice daily</p> <p><u>Migraine prophylaxis:</u> Twice daily</p> <p><u>MI:</u> Twice daily</p>	<p>During maintenance therapy for migraine prophylaxis, doses of 10 mg or 20 mg may be given once daily.</p> <p>Dosage reductions may be necessary in kidney and hepatic dysfunction as timolol is substantially excreted by the kidney (ie, risk of toxic reactions may be increased) and is partially metabolized in the liver.</p>
<b>Beta-blocker/Diuretic Combinations</b>				
Dutoprol (metoprolol succinate extended release/HCTZ)	Tablets	Oral	Once daily	<p>Safety and effectiveness in severe renal impairment (CrCL ≤ 30 mL/min) have not been established; no dose adjustment necessary in patients with moderate renal impairment.</p> <p>Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.</p>

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lopressor HCT (metoprolol tartrate/HCTZ)	Tablets	Oral	Daily in single or divided doses	While once-daily dosing is effective and can maintain a reduction in BP throughout the day, lower doses may not maintain a full effect at the end of the 24-hour period; larger or more frequent doses may be required.  Should be taken with or immediately following meals.
propranolol/HCTZ	Tablets	Oral	Twice daily	Use with caution in severe renal disease.
Tenoretic (atenolol/chlorthalidone)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required.  Atenolol can cause fetal harm when used in pregnancy and thiazide diuretics have caused adverse reactions for the fetus in pregnancy; use in pregnancy only if clearly needed.  Excreted in breast milk; use with caution. Clinically significant bradycardia and hypoglycemia in nursing infants has been reported.
Ziac (bisoprolol/HCTZ)	Tablets	Oral	Once daily	Use with caution when dosing/titrating patients with renal and hepatic impairment; discontinue use with progressive renal impairment.

See the current prescribing information for full details

Abbrev: BP = blood pressure, CrCL = creatinine clearance, ER = extended release, HCTZ=hydrochlorothiazide, IV = intravenous, MI = myocardial infarction, NYHA = New York Heart Association

\* Dosing from the package insert is summarized for completeness, but an IV formulation of atenolol is no longer marketed.

## CONCLUSION

- Beta-blockers are a group of drugs that block the effects of catecholamines on beta receptors.
- Beta-blockers have a range of FDA-approved indications as the agents within the class differ in pharmacologic and pharmacokinetic properties. Such differences may include adrenergic-receptor blocking activity, ISA, and lipophilicity.
- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of beta-blockers. All of the agents within the class, with the exception of sotalol, are FDA-approved for the treatment of HTN. Most guidelines recommend that the selection of an antihypertensive agent be based on compelling indications for use; the 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults recommends the use of beta-blockers as secondary agents after thiazide diuretics, ACE inhibitors, ARBs, and CCBs (*Whelton et al 2017*).
- The choice of a beta-blocker for a specific patient will depend on several factors. In addition to considering the clinical trial data and FDA-approved indications, patient diagnoses and comorbidities should be considered when selecting a product; for example:
  - Beta-blockers are best avoided in patients with asthma and chronic obstructive pulmonary disease; however, if no suitable alternatives exist, a beta<sub>1</sub>-selective agent is preferred.



- For patients with HF, bisoprolol, carvedilol, or metoprolol extended release should be considered as these have demonstrated a reduction in mortality; some guidelines recommend nebivolol as an option in certain HF patients (*Ponikowski et al 2016, Rosendorff et al 2015*).
- For patients with hepatic or renal disease, drugs that are not hepatically or renally eliminated, respectively, are preferred.
- For patients receiving concomitant therapy with a cytochrome (CYP) 2D6 inhibitor, beta-blockers that are not CYP2D6 substrates are preferred (*Clinical Pharmacology 2020*).
- For patients with HTN and acute coronary syndrome, initial therapy should include a short-acting beta<sub>1</sub>-selective beta-blocker without ISA (metoprolol tartrate or bisoprolol) (*Rosendorff et al 2015*).
- Most beta-blockers are available generically, including those that are recognized as effective for providing a mortality benefit in patients with HF (*Drugs@FDA 2020, Yancy et al 2013, Yancy et al 2017*). Available generic products will provide ample options for the majority of patients and clinical situations.
- The beta-blocker/diuretic combination products are FDA-approved for the treatment of HTN and are well-established for this indication.
- The beta-blocker/diuretic combinations are more effective compared to placebo and compared to the individual components given alone. There are currently no head-to-head trials comparing the various combination products to one another or any trials to demonstrate differences in clinical outcomes when the drug components are administered as separate agents concurrently versus the fixed-dose combination products.
- Many patients with HTN require more than 1 antihypertensive medication to achieve BP goals. Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence (*Mancia et al 2013*).
- HTN guidelines recommend combination therapy as a treatment option in patients who have BP that is not at goal with monotherapy (*James et al 2014, Mancia et al 2013, Weber et al 2014*).
- Most guidelines agree that beta-blockers are of particular value for hypertensive patients with certain co-morbid diseases, such as HF, post-MI, angina pectoris, coronary artery disease, and ventricular dysfunction (*Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014*). Other guidelines recommend beta-blockers for atrial fibrillation and diabetes (*Go et al 2014, Mancia et al 2013*). Diuretics also offer benefits in terms of diseases associated with edema, such as HF (*Go et al 2014, Mancia et al 2013, Weber et al 2014*). However, caution should be exercised as some guidelines do not recommend the use of beta-blockers in combination with a diuretic in patients at risk for diabetes as they have adverse effects associated with glucose metabolism (*Weber et al 2014*).

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