Therapeutic Class Overview
Beta-adrenergic Blocking Agents

INTRODUCTION

- Approximately 92.1 million American adults have at least 1 type of cardiovascular disease according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2018 update. From 2003 to 2015, mortality associated with cardiovascular disease declined 25.5% *(Benjamin et al 2018)*.
- 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 $beta_1$-receptors, which are predominantly found in the heart. Non-cardioselective beta-blockers also interact with $beta_2$-receptors found on smooth muscle in the lungs, blood vessels, and other tissues. The cardioselectivity of beta-blockers is dose dependent; therefore, $beta_2$ 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 2018)*. 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 2018)*.
  - Carvedilol and labetalol also block alpha-adrenergic receptors and may reduce peripheral resistance more than other beta-blockers *(Clinical Pharmacology 2018)*.
- 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) ≥ 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), heart failure, 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, has no generics currently on the market. Brand Hemangeol is an oral solution in strengths of 4.28 mg/mL (equivalent to 3.75 mg); however generic propranolol is available in strengths of 4 and 8 mg/mL oral solutions.
- 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 heart failure *(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 hypertension 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 hypertension. Patients with hypertension 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 hypertension. 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; however, bendroflumethiazide is not available as a single agent. 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
Single-Entity Beta-blockers	
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)*	✔ ‡
labetalol*	✔
Lopressor (metoprolol tartrate)	✔
pindolol*	✔
Tenormin (atenolol)	✔
timolol*	✔
Toprol XL (metoprolol succinate extended release)	✔
Beta-blocker/Diuretic Combinations	
Corzide (nadolol/bendroflumethiazide)	✔
Dutoprol (metoprolol succinate extended release/HCTZ)	-
Lopressor HCT (metoprolol tartrate/HCTZ)	✔
propranolol/HCTZ*	✔
Tenoretic (atenolol/chlorthalidone)	✔
Ziac (bisoprolol/HCTZ)	✔

*Branded Sectral (acebutolol), Kerlone (betaxolol), Zebeta (bisoprolol), Trandate (labetalol), Visken (pindolol), Blocadren (timolol), Inderal (propranolol), and Inderide (propranolol/HCTZ) are no longer marketed.
‡ Hemangeol (propranolol oral solution) , Inderal XL, and Innopran XL are brand-name only.
‖ Sotylize (sotalol oral solution) is brand-name only.

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. FDA-Approved Indications for Single-Entity Beta-blockers

Generic Name	Hypertension	Angina Pectoris	Cardiac Arrhythmias*	MI	Heart Failure	Pheochromocytoma	Migraine Prophylaxis	Hypertrophic Subaortic Stenosis	Proliferating Infantile Hemangioma requiring systemic therapy	Essential Tremor	Left Ventricular Dysfunction Following MI
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 cardiovascular mortality.
‖ May be used alone or in combination with other antihypertensive agents.
¶ Indicated for the management of essential hypertension.
# Indicated for the treatment of mild to severe chronic heart failure 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 cardiovascular 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 heart failure).
†† 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 cardiovascular 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) heart failure of ischemic, hypertensive or cardiomyopathic origin. Metoprolol succinate extended release capsules are indicated for the treatment of patients with heart failure to reduce the risk of cardiovascular mortality and heart failure-related hospitalization.
*** Indicated for the long term management of patients with angina pectoris.
††† Inderal XL and Innopran XL are indicated for the treatment of hypertension 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 cardiovascular 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 cardiovascular 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 2017, bisoprolol 2016, Betapace and Betapace AF 2016, Bystolic 2017, Coreg 2017, Coreg CR 2017, Corgard 2015, Hemangeol 2015, Inderal LA 2016, Inderal XL 2017, Innopran XL 2017, labetalol 2017, Lopressor 2017, metoprolol succinate extended release capsules 2018, pindolol 2016, propranolol solution 2017, propranolol tablets 2016, Sorine 2017, Sotylize 2015, Tenormin 2017, timolol 2006, Toprol XL 2016)

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 2016, Betapace and Betapace AF 2016, Sorine 2017, Sotylize 2015)

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

Drug	Hypertension
Corzide (nadolol/bendroflumethiazide)	✔ *
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 hypertension. 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: Corzide 2016, Dutoprol 2017, Lopressor HCT 2012, propranolol and HCTZ 2015, Tenoretic 2016, Ziac 2018)

- 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:

- Hypertension *(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)*
- Infantile hemangiomas *(Bauman et al 2014)*
- Essential tremor *(Calzetti et al 1981, Gironell et al 1999, Yetimalar et al 2005)*
- Migraine prophylaxis *(Ashtari et al 2008, Domingues et al 2009, 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 hypertension *(Czuriga et al 2003, Davidov et al 1988, Dhakam et al 2008, Fogari et al 1997)*.
- Trials have demonstrated cardiovascular 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, Freemantle et al 1999, Gottlieb et al 2001, Jonsson et al 2005, Olsson et al 1992)*.
- For the treatment of heart failure, a survival benefit has been demonstrated with bisoprolol, carvedilol, and sustained-release metoprolol succinate; however, only carvedilol and metoprolol succinate are FDA-approved for the treatment of heart failure. 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 heart failure, nebivolol demonstrated a significant improvement in a composite measure of death or cardiovascular 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 heart failure; 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 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 meta-analysis 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 heart failure *(Brophy et al 2001, Chatterjee et al 2013, Lechat et al 1998, Whorlow et al 2000)*.

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, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1983).

- 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 cardiovascular 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 cardiovascular 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	▪ Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is > 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbrv: ASCVD= atherosclerotic cardiovascular disease, BP = blood pressure, CKD= chronic kidney disease, CVD= cardiovascular disease, DBP= diastolic blood pressure, DM=diabetes mellitus, HTN= hypertension, 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 heart failure.
    - 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 heart failure 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 hypertension 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, Mancia et al 2013, Weber et al 2014, Whelton et al 2017)*. However, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines also recommend beta-blockers as a first line therapy option *(Mancia et al 2013)*.
  - In the treatment of severe hypertension in pregnancy, labetalol is outlined as an option with consideration of maternal and fetal side effects *(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, heart failure, acute coronary syndrome, and in the management of angina pectoris *(Go et al 2014, Mancia et al 2013, Rosendorff et al 2015, Weber et al 2014)*.
- The beta-blockers are also a mainstay of heart failure 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 are the only 2 beta-blockers FDA-approved for the treatment of heart failure, 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 heart failure in patients with a systemic right ventricle (RV) are lacking, despite the high incidence of late clinical heart failure and sudden death in this population. Use of conventional heart failure 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 cardiovascular 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 coronary artery bypass grafting (CABG), valvular heart disease, and hypertrophic cardiomyopathy *(Amsterdam et al 2014[a,b], Fihn et al 2012, Fihn et al 2014, Gersh et al 2011,Ibanez et al 2018, January et al 2014[a,b], Jneid et al 2012, Montalescot et al 2013, 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, Windecker et al 2014)*.
- Metoprolol, propranolol, and timolol are established as effective for migraine prevention *(Silberstein et al 2012, Snow et al 2002)*.
- Propranolol is the only beta-blocker 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)*.
- Treatment guidelines for infantile hemangioma are not available; however, consensus recommendations state that therapy must be individualized. Oral propranolol may be considered in patients with ulcerative hemangiomas, impairment of a vital function (ocular compromise or airway obstruction), or in cases with a risk of permanent disfigurement. Monitoring of infants for adverse events is required *(Drolet et al 2013)*.

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 heart failure or cardiogenic shock. Based on their ability to block $beta_2$ 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, and timolol, noting that severe exacerbation of angina and the occurrence of MI and

ventricular 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 ischemic heart disease, 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 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.
  - 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 include patients with sinus bradycardia and patients with sinus pauses or arrest.
  - Lopressor HCT is contraindicated in those with severe peripheral arterial circulatory disorders.
  - Corzide and propranolol/HCTZ are contraindicated in patients with bronchial asthma.
- Boxed warning for Corzide, Dutoprol, Lopressor HCT, and propranolol/HCTZ: Do not discontinue abruptly; withdraw gradually with appropriate monitoring to avoid potential exacerbation of ischemic heart disease. This is also a warning for Tenoretic and Ziac (although not boxed).
- Avoid in overt heart failure; use with caution in patients with controlled heart failure.
- Avoid in patients with bronchospastic disease. Low doses of $beta_1$ 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 calcium channel blockers, digoxin, or clonidine increases the risk. The drug also has additional warnings for acute renal failure in patients with chronic kidney disease, severe heart failure, or volume depletion when also taking HCTZ-containing drugs; 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 (Corzide, propranolol/HCTZ, and Tenoretic) are not specifically listed in the prescribing information; however, adverse reactions are known based on experience with their components. Notable adverse reactions include heart failure, 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
Single-Entity Beta-blockers				
Acebutolol	Capsules	Oral	Cardiac arrhythmias (ventricular): Twice daily Hypertension: 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	Angina pectoris: Once daily Hypertension: Once daily Acute MI: 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 from the hospital.	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	Hypertension: Once daily	Dosage adjustment in renal impairment is required. Consideration should be given to reduction in the starting

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				dose to 5 mg in elderly patients.
Bisoprolol	Tablets	Oral	Hypertension: Once daily	Dosage adjustment in renal and hepatic impairment is required.
Carvedilol	ER capsules, tablets	Oral	Heart failure: ER capsule: Once daily Tablet: Twice daily Hypertension: ER capsule: Once daily Tablet: Twice daily Left ventricular dysfunction following MI: ER capsule: Once daily Tablet: Twice daily	Patients controlled with immediate release (IR) tablets may be switched to ER capsules (see prescribing information for details). When switching from the higher doses of IR carvedilol to ER, a lower starting dose is recommended for the elderly. Contraindicated in severe hepatic dysfunction. 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. Tablet: Take with food.
Labetalol	Tablets	Oral	Hypertension: Twice daily	Dose adjustment is required in the elderly. Use with caution in hepatic dysfunction; metabolism of the drug may be diminished.
Metoprolol	ER tablets (succinate), ER capsules (succinate)§, tablets (tartrate)	Oral	Angina pectoris: ER tablet or ER capsule: Once daily Tablet: Daily in 2 divided doses Heart failure: ER tablet (NYHA Class II): Once daily [start with 25 mg/day] ER tablet (severe heart failure): Once daily [start with 12.5 mg/day]	A hepatic dosage adjustment may be necessary; initiate at low doses with cautious gradual titration. ER tablet or ER capsule: Dosing recommendations are available for pediatric hypertensive patients ≥ 6 years of age; product is not recommended in patients < 6 years. ER tablet: Take with or immediately after meals. ER

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			ER capsule: once daily [start with 25 mg/day] Hypertension: ER tablet or ER capsule: Once daily Tablet: Daily in single or divided doses MI: 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	tablets are scored and can be divided, but not crushed or chewed. ER capsule: swallow whole or sprinkle capsule contents over soft food; mix contents with water for nasogastric tube administration ER capsule: 1 to 1 dose conversion with ER tablet Tablet: Take with or immediately after meals. Do not chew.
Nadolol	Tablets	Oral	Angina pectoris: Once daily Hypertension: Once daily	Dosage adjustment in renal impairment is required.
Nebivolol	Tablets	Oral	Hypertension: Once daily	Dosage adjustment in renal and hepatic impairment is required.
Pindolol	Tablets	Oral	Hypertension: 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	Angina pectoris: ER capsule (Inderal LA): Once daily Oral solution, tablet: Daily in 2, 3 or 4 divided doses Cardiac arrhythmias (atrial fibrillation): Oral solution, tablet: Three to 4 times daily before meals and at bedtime Essential tremor: Oral solution, tablet: Twice daily Hypertension:	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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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 Hypertrophic subaortic stenosis: Oral solution, tablet: Three to 4 times daily before meals and at bedtime ER capsule (Inderal LA): Once daily Infantile hemangioma: Oral solution (Hemangeol): Twice daily Migraine prophylaxis: Oral solution, tablet: Daily in divided doses ER capsule (Inderal LA): Once daily MI: Oral solution, tablet: Twice or 3 times daily Pheochromocytoma: Oral solution, tablet (operable 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	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.
Sotalol	Tablets (Betapace, Betapace AF, Sorine), Oral solution (Sotylize)	Oral	Cardiac arrhythmias (maintenance of normal sinus rhythm in patients	Pediatric dosing is available for the treatment of cardiac arrhythmias (ventricular and

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			with symptomatic atrial fibrillation/atrial flutter): Tablet (Betapace, Betapace AF, Sorine): Twice daily Oral solution (Sotylize): Once or twice daily based on renal function Cardiac arrhythmias (ventricular): Tablet (Betapace, Betapace AF, Sorine): Twice daily Oral solution (Sotylize): Once or twice daily based on renal function	symptomatic atrial fibrillation/ atrial flutter). Dosage adjustment in renal impairment is required. For treatment of atrial fibrillation or flutter, use is contraindicated if creatinine clearance is < 40 mL/min. See the Betapace prescribing information for instructions on compounding an oral solution from the tablets.
Timolol	Tablets	Oral	Hypertension: Twice daily Migraine prophylaxis: Twice daily MI: Twice daily	During maintenance therapy for migraine prophylaxis, doses of 10 mg or 20 mg may be given once daily. 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.
Beta-blocker/Diuretic Combinations				
Corzide (nadolol/ bendroflumethiazide)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required.
Dutoprol (metoprolol succinate extended release/ HCTZ)	Tablets	Oral	Once daily	Safety and effectiveness in severe renal impairment (creatinine clearance < 30 mL/min) have not been established; no dose adjustment necessary in patients with moderate renal impairment. Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

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.

§Not yet launched.
NYHA = New York Heart Association

See the current prescribing information for full details

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 hypertension. 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 $beta_1$-selective agent is preferred.
  - For patients with heart failure, bisoprolol, carvedilol, or sustained release metoprolol should be considered as these have demonstrated a reduction in mortality; although some guidelines recommend nebivolol as an option in certain heart failure 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 CYP2D6 inhibitor, beta-blockers that are not CYP2D6 substrates are preferred *(Clinical Pharmacology 2018)*.
  - For patients with hypertension and acute coronary syndrome, initial therapy should include a short-acting $beta_1$-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 heart failure *(Drugs@FDA 2018, 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 hypertension 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 hypertension 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)*.
- Hypertension guidelines recommend combination therapy as a treatment option in patients who have BP that is not at goal *(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 heart failure, 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 heart failure *(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)*.

REFERENCES

- Acebutolol [package insert], Bridgewater, NJ: Amneal Pharmaceuticals of New York, LLC; May 2017.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014[a];64(24):e139-228.
- Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014[b];130(25):2354-94.
- Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. *Acta Neurol Scand*. 2008;118:301-5.
- Bangalore S, Bhatt DL, Steg PG, et al. ß-blockers and cardiovascular events in patients with and without myocardial infarction: Post hoc analysis from the CHARISMA trial. *Circ Cardiovasc Qual Outcomes*. 2014; 7(6):872-81.
- Bauman NM, McCarter RJ, Guzzeta PC. Propranolol vs prednisolone for symptomatic proliferating infantile hemangiomas. *JAMA Otolaryngal Head Neck Surg*. 2014;140(4):323-30.
- Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics – 2018 update: a report from the American Heart Association. *Circulation*. 2018;137(12):e67-e492. doi: 10.1161/CIR.0000000000000558.
- Betaxolol [package insert], Newtown, PA: KVK-TECH, INC.; December 2017.
- Betapace and Betapace AF [package insert], Zug, Switzerland: Covis Pharma; May 2016.
- Bisoprolol [package insert], Princeton, NJ: Eon Labs Inc.; September 2016.

- Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94(11):2807-16.
- Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Ann Intern Med*. 2001;134(7):550-60.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(5):1545-88.
- Bystolic [package insert], Irvine, CA: Allergan USA, Inc.; November 2017.
- Calzetti S, Findley LJ, Gresty MA, et al. Metoprolol and propranolol in essential tremor: a double-blind, controlled study. *J Neurol Neurosurg Psychiatry*. 1981;44(9):814-9.
- Chatterjee S, Biondi-Zoccai G, Abbate A, et al. Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. *BMJ*. 2013;346:f55.
- CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;90(4):1765-73.
- CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet*. 1999;353(9146):9-13.
- Clinical Pharmacology Web site. http://www.clinicalpharmacology-ip.com/default.aspx. Accessed April 17, 2018.
- Coreg [package insert], Research Triangle Park, NC: GlaxoSmithKline LLC; September 2017.
- Coreg CR [package insert], Research Triangle Park, NC: GlaxoSmithKline LLC; September 2017.
- Corgard [package insert], Louisville, KY: US WorldMeds, LLC; December 2015.
- Corzide prescribing information. New York, NY: Pfizer Laboratories Div Pfizer Inc; July 2016.
- Czuriga I, Riecansky I, Bodnar J, et al. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: the Nebivolol, Bisoprolol Multicenter Study (NEBIS). *Cardiovasc Drugs Ther*. 2003;17(3):257-63.
- Dafgard T, Forsen B, Lindahl T. Comparative study of hydrochlorothiazide and a fixed combination of metoprolol and hydrochlorothiazide essential hypertension. *Ann Clin Res*. 1981;13(Suppl 30):S37-S44.
- Dahlöf B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet*. 1991;338(8778):1281-5.
- Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357(9266):1385-90.
- Davidov ME, Glazer N, Wollam G, et al. Comparison of betaxolol, a new beta 1-adrenergic antagonist, to propranolol in the treatment of mild to moderate hypertension. *Am J Hypertens*. 1988;1(3 Pt 3):206S-210S.
- de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40:1273-84.
- de Leeuw PW, Notter T, Zilles P. Comparison of different fixed antihypertensive combination drugs: a double-blind, placebo-controlled parallel group study. *J Hypertens*. 1997;15(1):87-91.
- Dhakam Z, Yasmin, McEniery CM, et al. A comparison of atenolol and nebivolol in isolated systolic hypertension. *J Hypertens*. 2008;26(2):351-6.
- Dietz R, Dechend R, Yu CM, et al. Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension. *J Renin Angiotensin Aldosterone Syst*. 2008;9(3):163-75.
- Di Lenarda A, Sabbadini G, Salvatore L, et al. Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol. The Heart-Muscle Disease Study Group. *J Am Coll Cardiol*. 1999;33(7):1926-34.
- DiNicolantonio JJ, Beavers CJ, Menezes AR, et al. Meta-analysis comparing carvedilol versus metoprolol for the prevention of postoperative atrial fibrillation following coronary artery bypass grafting. *Am J Cardiol*. 2014;113(3):565-9.
- Domingues RB, Piraja da Silva AL, Domingues SA, et al. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. *Arg Neuropsiquiatr*. 2009;67(4):973-7.
- Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics*. 2013;131(1):128-140.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 17, 2018.
- Dutoprol [package insert], St. Michael, Barbados: Concordia Pharmaceuticals Inc; August 2017.
- Facts and Comparisons eAnswers [database online]. http://online.factsandcomparisons.com/index.aspx. Accessed April 17, 2018.
- Fogari R, Zoppi A. Half-strength atenolol-chlorthalidone combination (Tenoretic mite) in the treatment of elderly hypertensive patients. *Int J Clin Pharmacol Ther Toxicol*. 1984;22(7):386-93.
- Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:3097–3137.
- Fihn SD, Blankenship J, Alexander K, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014 ;64(18):1929-49.
- Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215-225.
- Fogari R, Zoppi A, Lazzari P, et al. Comparative effects of nebivolol and atenolol on blood pressure and insulin sensitivity in hypertensive subjects with type II diabetes. *J Hum Hypertens*. 1997;11(11):753-7.
- Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318(7200):1730-7.
- Frishman WH, Bryzinski BS, Coulson LR, et al. A multifactorial trial design to assess combination therapy in hypertension. Treatment with bisoprolol and hydrochlorothiazide. *Arch Intern Med*. 1994;154(13):1461-8.

- Frishman WH, Burris JF, Mroczek WJ, et al. First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J Clin Pharmacol*. 1995;35(2):182-8.
- Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/ACA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e783-e831.
- Giles TD, Weber MA, Basile J, et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet*. 2014;383(9932):1889-98.
- Gironell A, Kulisevsky J, Barbanoj M, et al. A randomized placebo-controlled comparative trial of gabapentin and propranolol in essential tremor. *Arch Neurol*. 1999;56(4):475-80.
- Go AS, Bauman M, King SM, et al. An Effective Approach to High Blood Pressure Control: A Science Advisory from the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention (AHA/ACC/CDC). *J Am Coll Cardiol*. 2014;63(12):1230-1238.
- Goldstein S, Fagerberg B, Hjalmarson A, et al. Metoprolol controlled release/extended release in patients with severe heart failure. *J Am Coll Cardiol*. 2001;38:932-8.
- Gottlieb SS, McCarter RJ. Comparative effects of three beta blockers (atenolol, metoprolol, and propranolol) on survival after acute myocardial infarction. *Am J Cardiol*. 2001;87(7):823-6.
- Gradman AH. Strategies for combination therapy in hypertension. *Curr Opin Nephrol Hypertens*. 2012;21:486-491.
- Greathouse M. Nebivolol efficacy and safety in patients with stage I-II hypertension. *Clin Cardiol*. 2010;33(4):E20-E7.
- Hamaad A, Lip GYH, Nicholls D, et al. Comparative dose titration response to the introduction of bisoprolol or carvedilol in stable chronic systolic heart failure. *Cardiovasc Drugs Ther*. 2007;21:437-44.
- Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611–616.
- Hemangeol [package insert], Parsippany, NJ: Pierre Fabre Pharmaceuticals, Inc.; May 2015.
- Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segmented elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177. doi: 10.1093/eurheartj/ehx393.
- Inderal LA [package insert], Baudette, MN: ANI Pharmaceuticals, Inc.; October 2016.
- Inderal XL [package insert], Baudette, MN: ANI Pharmaceuticals, Inc.; December 2017.
- Innopran XL [package insert], Baudette, MN: ANI Pharmaceuticals, Inc.; December 2017.
- James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). [Internet]. *JAMA*.2014;311(5):507-20.
- January CT, Wann LS, Alpert J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014[a];64(21):2246-80.
- January CT, Wann LS, Alpert J, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014[b];64(21):e1-e76.
- Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2012;126:875–910.
- Jonsson G, Abdelnoor M, Müller C, et al A. A comparison of the two beta-blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients. *Cardiology*. 2005;103(3):148-55.
- Krum H, Sackner-Berstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure (abstract). *Circulation*. 1995;92:1499-506.
- Kveiborg B, Major-Petersen A, Christiansen B, et al. Carvedilol in the treatment of chronic heart failure: Lessons from the Carvedilol or Metoprolol European Trial. *Vasc Health Risk Manag*. 2007;3(1):31-37.
- Labetalol [package insert], Chestnut Ridge, NY: Par Pharmaceutical, Inc.; March 2017.
- Lechat P, Packer M, Chalon S, et al. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation*. 1998;98(12):1184-91.
- Leonetti G, Pasotti C, Capra A. Low-dose atenolol-chlorthalidone combination for treatment of mild hypertension. *Int J Clin Pharmacol Ther Toxicol*. 1986;24(1):43-7.
- Lewin AJ, Lueg MC, Targum S, et al. A clinical trial evaluating the 24-hour effects of bisoprolol/hydrochlorothiazide 5 mg/6.25 mg combination in patients with mild to moderate hypertension (abstract). *Clin Cardiol*. 1993;16(10):732-6.
- Liedholm H, Ursing D. Antihypertensive effect and tolerability of two fixed combination of metoprolol and hydrochlorothiazide followed by a long-term tolerance study with one combination. *Ann Clin Res*. 1981;13(Suppl 30):S45-S53.
- Lopressor [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; September 2017.
- Lopressor HCT [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; October 2012.
- Lui HK, Lee G, Dhurandhar R, et al. Reduction of ventricular ectopic beats with oral acebutolol: a double-blind, randomized crossover study. *Am Heart J*. 1983;105:722-6.
- Maack C, Elter T, Nickenig G, et al. Prospective crossover comparison of carvedilol and metoprolol in patients with chronic heart failure. *J Am Coll Cardiol*. 2001 Oct;38(4):939-46.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159-219.
- Materson BJ, Cushman WC, Goldstein G, et al. Treatment of hypertension in the elderly: I. Blood pressure and clinical changes: results of a Department of Veterans Affairs cooperative study. *Hypertension*. 1990;15(4):348-60.

- MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) *Lancet*. 1999;353(9169):2001-7.
- Metoprolol succinate extended-release capsule [package insert]. New Brunswick, NJ: Ohm Laboratories Inc; January 2018.
- Metra M, Giubbini R, Nodari S, et al. Differential effects of beta-blockers in patients with heart failure: A prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102(5):546-51.
- Montalescot G, Sechtem U, Achenback S, et al. 2013 ESC Guidelines on the management of stable coronary artery disease: The Task Force for the management of stable coronary artery disease of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34:2949-3003.
- Neutel JM, Smith DHG, Gradman AH. Adding nebivolol to ongoing antihypertensive therapy improves blood pressure and response rates in patients with uncontrolled stage I-II hypertension. *J Hum Hypertens*. 2010;24:64-73.
- Nishimura R, Otto C, Bonow R, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014[a];63(22):2438-88.
- Nishimura R, Otto C, Bonow R, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014[b];63(22):e57-185.
- Nishimura R, Otto C, Bonow R, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2017;135(25):e1159-e1195. doi: 10.1161/CIR.0000000000000503.
- Niskanen L, Hedner T, Hansson L, et al. CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. *Diabetes Care*. 2001;24(12):2091-96.
- Nissinen A, Tuomilehto J. Evaluation of the antihypertensive effect of atenolol in fixed or free combination with chlorthalidone. *Pharmatherapeutica*. 1980;2(7):462-8.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:e362–e425.
- Olsson G, Wikstrand J, Warnold I, et al. Metoprolol-induced reduction in postinfarction mortality: pooled results from five double-blind randomized trials. *Eur Heart J*. 1992;13(1):28-32.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 17, 2018.
- Packer M, Antonopoulos GV, Berlin JA, et al. Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: results of a meta-analysis. *Am Heart J*. 2001[a];141(6):899-907.
- Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996; 334(21):1349-55.
- Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001[b];344(22):1651-8.
- Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation*. 2002;106:2194-99.
- Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the management of adult patients with supraventricular tachycardia. *Circulation*. 2016;133(14):e506-74.
- Pandhi P, Sethi V, Sharma BK, et al. Double blind cross-over clinical trial of acebutolol and propranolol in angina pectoris. *Int J Clin Pharmacol Ther Toxicol*. 1985;23(11):598-600.
- Pindolol [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; November 2016.
- Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC); Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;18(8):891-975.
- Poole-Wilson PA, Swedberg K, Cleland JG, et al; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362(9377):7-13.
- Priori SG, Blomstrom-Lundqvist, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*. 2015;36(41):2793-2867.
- Propranolol solution [package insert], Eatontown, NJ: West Ward Pharmaceuticals Corp.; May 2017.
- Propranolol tablet [package insert], Hayward, CA: Impax Generics; May 2016.
- Propranolol hydrochloride and hydrochlorothiazide [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; June 2015.
- Rao BS, Taraknath VR, Sarma T. A double blind controlled study of propranolol and Cyproheptadine in migraine prophylaxis. *Neurol India*. 2000;48(3):223-6.
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
- Rosendorff C, Lackland DT, Allison M, et al. Treatment of Hypertension in Patients with Coronary Artery Disease: A Scientific Statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension (AHA/ACC/ASH). *J Am Coll Cardiol.* 2015;65(18):1998-2038.
- Ruwald MH, Ruwald AC, Jons C, et al. Effect of metoprolol versus carvedilol on outcomes in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol*. 2013;61(14):1518-26.
- Sanderson JE, Chan SK, Yip G, et al. Beta-blockade in heart failure: a comparison of carvedilol with metoprolol. *J Am Coll Cardiol*. 1999;34(5):1522-8.
- Schellenberg R, Lichtenthal A, Wohling H, et al. Nebivolol and metoprolol for treating migraine: An advance in beta-blocker treatment? *Headache*. 2008;48(1):118-25.

- Seidl K, Hauer B, Schwick NG, et al. Comparison of metoprolol and sotalol in preventing ventricular tachyarrhythmias after the implantation of a cardioverter/defibrillator. *Am J Cardiol*. 1998;82(6):744-8.
- Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78;1337.
- Smilde JG. Comparison of the antihypertensive effect of a double dose of metoprolol versus the addition of hydrochlorothiazide to metoprolol. *Eur J Clin Pharmacol*. 1983;25(5):581-3.
- Snow V, Weiss K, Wall EM, et al. American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med*. 2002;137(10):840-9.
- Sorine [package insert], Maple Grove, MN: Upsher-Smith Laboratories, Inc.; June 2017.
- Sotylize [package insert], Atlanta, GA: Arbor Pharmaceuticals, LLC; July 2015.
- Stevens JD, Mullane JF. Propranolol-hydrochlorothiazide combination in essential hypertension. *Clin Ther*. 1982;4(6):497-509.
- Stoschitzky K, Stoschitzky G, Brussee H, et al. Comparing beta-blocking effects of bisoprolol, carvedilol and nebivolol. *Cardiology*. 2006;106(4):199-206.
- Stout KK, Broberg CS, Book WM, et al.; American Heart Association Council on Clinical Cardiology, Council on Functional Genomics and Translational Biology, and Council on Cardiovascular Radiology and Imaging. Chronic Heart Failure in Congenital Heart Disease: A Scientific Statement from the American Heart Association. *Circulation*. 2016;133(8):770-801.
- Tenoretic [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; May 2016.
- Tenormin [package insert], Pine Brook, NJ: Almatica Pharma, Inc.; November 2017.
- Tfelt-Hansen P, Standnes B, Kangasneimi P, et al. Timolol vs propranolol vs placebo in common migraine prophylaxis a double-blind multicenter trial. *Acta Neurol Scand*. 1984;69:1-8.
- Timolol [package insert], Morgantown, WV: Mylan Pharmaceuticals Inc.; August 2006.
- Toprol XL [package insert], Princeton, NJ: Aralez Pharmaceuticals US Inc.; December 2016.
- Van Bortel LM, Bulpitt CJ, Fici F. Quality of life and antihypertensive effect with nebivolol and losartan. *Am J Hypertens*. 2005;18(8):1060-6.
- van der Does R, Hauf-Zachariou U, Pfarr E, et al. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. *Am J Cardiol*. 1999;83(5):643-9.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Efficacy of nadolol alone and combined with bendroflumethiazide and hydralazine for systemic hypertension. *Am J Cardiol*. 1983;52(10):1230-37.
- Veterans Administration Cooperative Study Group on Antihypertensive Agents. Propranolol in the treatment of essential hypertension. *JAMA*. 1977;237(21):2303-10.
- Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;342(8885):1441-6.
- Wald DS, Law M, Mills S, et al. A 16-week, randomized, double-blind, placebo-controlled, crossover trial to quantify the combined effect of an angiotensin-converting enzyme inhibitor and a beta-blocker on blood pressure reduction. *Clin Ther*. 2008;30(11):2030-9.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH). *J Hypertens*. 2014;32(1):3-15.
- Weiss R, Ferry D, Pickering E, et al. Effectiveness of three different doses of carvedilol for exertional angina. Carvedilol-Angina Study Group. *Am J Cardiol*. 1998;82(8):927-31.
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2017;70(6):1-192.
- Whorlow SL, Krum H. Meta-analysis of effect of beta-blocker therapy on mortality in patients with New York Heart Association class IV chronic congestive heart failure. *Am J Cardiol*. 2000;86(8):886-9.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541-619.
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol*. 2013;62(16):e147-239.
- Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Failure Society of America. *J Card Fail*. 2017;23(8):628-651.
- Yetimalar Y, Gulumser I, Kurt T, et al. Olanzapine versus propranolol in essential tremor. *Clin Neurol Neurosurg*. 2005;108(1):32-5.
- Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor; Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2011;77(19):1752-5.
- Ziac [package insert], North Wales, PA: Teva Women's Health, Inc.; March 2018.

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