Therapeutic Class Overview
Beta-adrenergic antagonists (single-entity)

- **Therapeutic Class Overview/Summary:** The beta-adrenergic blocking agents (β-blockers) are Food and Drug Administration (FDA)-approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-26] The β-blockers differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-26] There are at least three distinct types of β receptors distributed throughout the body (β1, β2, and β3). β1-receptors are located predominantly in the heart and kidneys. β2-receptors are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β3-receptors are located in fat cells. β-blockers primarily exert their effects through a blockade of β1 and β2 receptor subtypes. Agents that have a greater affinity for β1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease because they produce less inhibition of β2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β2 blockade can occur at higher doses. Carvedilol and labetalol also block α-adrenergic receptors.[27-28]

  Current clinical guidelines identify β-blockers as effective in many indications. Their place in therapy varies depending on indication and other patient specific factors. Specific treatment guidelines are summarized in Table 12.[29-61] The beta-adrenergic blocking agents that are included in this review are listed in Table 1 and comparative information on cardioselectivity is highlighted in Table 2. This review encompasses all dosage forms and strengths for the single-entity products. A significant majority of these agents are available as a generic product.

Table 1. Current Medications Available in the Therapeutic Class[1-26]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Acebutolol HCl (Sectral®*)	Management of ventricular premature beats; hypertension alone or in combination with other antihypertensives	Capsule: 200 mg 400 mg	a
Atenolol (Tenormin®*)	To decrease angina frequency and increase exercise tolerance due to coronary atherosclerosis; hypertension alone or in combination with other antihypertensives; hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Tablet: 25 mg 50 mg 100 mg	a
Betaxolol HCl (Kerlone®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 10 mg 20 mg	a
Bisoprolol fumarate (Zebeta®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 5 mg 10 mg	a
Carvedilol (Coreg®*)	Essential hypertension, alone or in combination with other antihypertensives; mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations; reduce cardiovascular mortality in clinically stable patients who have survived the acute phase	Tablet: 3.125 mg 6.25 mg 12.5 mg 25 mg	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)		
Carvedilol Phosphate (Coreg CR)	Essential hypertension, alone or in combination with other antihypertensives; mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations; reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)	Extended-release capsule: 10 mg 20 mg 40 mg 80 mg	-
Esmolol (Brevibloc®*)	Intraoperative and Postoperative Tachycardia and/or Hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia and in the postoperative period; Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia, short term control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances	Injection: 10 mg/mL IV solution (Brevibloc®): 10 mg/mL 20 mg/mL	a
Labetalol HCl (Trandate®*)	Hypertension alone or in combination with other antihypertensives (tablet); Hypertension, control of blood pressure in severe hypertension (injection)	Injection: 5 mg/mL Tablet: 100 mg 200 mg 300 mg	a
Metoprolol tartrate (Lopressor®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with other antihypertensives; Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Injection: 5 mg/5 mL Tablet: 25 mg 50 mg 100 mg	a
Metoprolol succinate (Toprol XL®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with other antihypertensives; Stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin; Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality	Extended-release tablet: 25 mg 50 mg 100 mg 200 mg	a
Nadolol (Corgard®*)	Angina, long-term maintenance treatment; Hypertension alone or in combination with	Tablet: 20 mg	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	other antihypertensives	40 mg 80 mg	
Nebivolol HCl (Bystolic®*)	Hypertension alone or in combination with other antihypertensives	Tablet: 2.5 mg 5 mg 10 mg 20 mg	-
Penbutolol sulfate (Levatol®)	Mild to moderate arterial hypertension alone or in combination with other antihypertensives	Tablet: 20 mg	-
Pindolol	Hypertension alone or in combination with other antihypertensives	Tablet: 5 mg 10 mg	a
Propranolol HCl (Hemangeol®, Inderal LA®*, Inderal XL®, Innopran XL®)	To decrease angina frequency and increase exercise tolerance due to coronary atherosclerosis (24-hour capsule); Persistent premature ventricular extrasystoles that impair the well-being of the patient and do not respond to conventional measures (injection); Short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate (injection); To abolish tachyarrhythmias due to excessive catecholamine action during anesthesia when other measures fail (injection); To control ventricular rate in life-threatening digitalis-induced arrhythmias (injection); To control ventricular rate in patients with atrial fibrillation and a rapid ventricular response(tablet); Hypertension alone or in combination with other antihypertensives; Improves NYHA functional class in symptomatic patients with hypertropic subaortic stenosis (24-hour capsule); Reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable (tablet); Adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors (tablet); Familial or hereditary essential tremor (injection); Treatment of proliferating infantile hemangioma requiring systemic therapy (oral solution); Prophylaxis of migraine headache (24-hour capsule)	capsule: 60 mg 80 mg 120 mg 160 mg Injection: 1 mg/mL Oral solution: 20 mg/5 mL 40 mg/5 mL Oral Solution (Hemangeol®): 4.28 mg/mL Tablet: 10 mg 20 mg 40 mg 60 mg 80 mg	a
Sotalol HCl (Betapace®*, Betapace AF®*, Sotylize®,	Documented ventricular arrhythmias that in the judgement of the physician are life-threatening; Maintenance of normal sinus rhythm in patients with symptomatic atrial	Injection: 150 mg/10 mL Oral Solution	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Sorine®†)	fibrillation/atrial flutter who are currently in sinus rhythm	(Sotylize®): 5 mg/mL Tablet: 80 mg 120 mg 160 mg 240 mg	
Timolol Maleate	Hypertension alone or in combination with other antihypertensives; Reduce cardiovascular mortality and reinfarction in patients who have survived the acute phase of myocardial infarction and are clinically stable; Prophylaxis of migraine headache	Tablet: 5 mg 10 mg 20 mg	a

HCl=hydrochloride
* Generic available in at least one formulation
† Branded generic product

Evidence-based Medicine

- Despite the extensive experience with β-blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with an arrhythmia, hypertension, or angina pectoris and other indications.[63-185]
- The safety and efficacy of sotalol hydrochloride oral solution (Sotylize®) was established using pre-existing clinical trial data used for the FDA-approval sotalol hydrochloride (Betapace®, Betapace AF®).[22-25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - β-blockers as effective in many indications. Their place in therapy varies depending on indication and other patient specific factors.
- Other Key Facts:
  - β-blockers primarily exert their effects through a blockade of β1 and β2 receptor subtypes. Agents that have a greater affinity for β1 receptors are considered to be cardioselective.
    - These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease.[27-28]
  - Carvedilol and labetalol also block α-adrenergic receptors.[27-28]

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Therapeutic Class Review
Beta-adrenergic antagonists (single-entity)

Overview/Summary

The beta-adrenergic blocking agents (β-blockers) are Food and Drug Administration (FDA)-approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-26] The β-blockers differ with regards to their adrenergic-receptor blocking, membrane stabilizing and intrinsic sympathomimetic activities, as well as lipophilicity.[1-26] There are at least three distinct types of β receptors distributed throughout the body (β1, β2, and β3). β1 receptors are located predominantly in the heart and kidneys. β2 receptors are located in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β3-receptors are located in fat cells. β-blockers primarily exert their effects through a blockade of β1 and β2 receptor subtypes. Agents that have a greater affinity for β1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease because they produce less inhibition of β2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β2 blockade can occur at higher doses with these agents. Carvedilol and labetalol also block α-adrenergic receptors.[27-28]

Current clinical guidelines identify β-blockers as effective in many indications. Their place in therapy varies depending on indication and other patient specific factors. Specific treatment guidelines are summarized in Table 12.[29-61] The beta-adrenergic blocking agents that are included in this review are listed in Table 1 and comparative information on cardioselectivity is highlighted in Table 2. This review encompasses all dosage forms and strengths for the single-entity products. A significant majority of these agents are available as a generic product.

Medications

Table 1. Medications Included Within Class Review[1-26]

Generic Name (Trade name)	Medication Class	Generic Availability
Acebutolol HCl (Sectral®*)	Beta-adrenergic antagonist	a
Atenolol (Tenormin®*)	Beta-adrenergic antagonist	a
Betaxolol HCl (Kerlone®*)	Beta-adrenergic antagonist	a
Bisoprolol fumarate (Zebeta®*)	Beta-adrenergic antagonist	a
Carvedilol (Coreg®*)	Beta-adrenergic antagonist	a
Carvedilol Phosphate (Coreg CR)	Beta-adrenergic antagonist	-
Esmolol (Brevibloc®*)	Beta-adrenergic antagonist	a
Labetalol HCl (Trandate®*)	Beta-adrenergic antagonist	a
Metoprolol tartrate (Lopressor®*)	Beta-adrenergic antagonist	a
Metoprolol succinate (Toprol XL®*)	Beta-adrenergic antagonist	a
Nadolol (Corgard®*)	Beta-adrenergic antagonist	a
Nebivolol HCl (Bystolic®)	Beta-adrenergic antagonist	-
Penbutolol sulfate (Levatol®)	Beta-adrenergic antagonist	-
Pindolol	Beta-adrenergic antagonist	a
Propranolol HCl (Hemangeol®, Inderal LA®*, Inderal XL®, Innopran XL®)	Beta-adrenergic antagonist	a
Sotalol HCl (Betapace®*, Betapace AF®*, Sotylize®, Sorine®†)	Beta-adrenergic antagonist	a
Timolol Maleate	Beta-adrenergic antagonist	a

*Generic available in at least one formulation
†Branded generic product
HCL=hydrochloride

Table 2. Selected Pharmacologic Properties of the Beta-Adrenergic Blocking Agents[1-28]

Generic Name(s)	Adrenergic-Receptor Blocking Activity	Membrane Stabilizing Activity	Intrinsic Sympathomimetic Activity
Acebutolol	β_1*	+†	+
Atenolol	β_1*	0	0
Betaxolol	β_1*	+	0
Bisoprolol	β_1*	0	0
Carvedilol	α_1 - β_1 - β_2	++	0
Esmolol	Not reported	Not reported	Not reported
Labetalol	α_1 - β_1 - β_2	0	+
Metoprolol	β_1*	0†	0
Nadolol	β_1 - β_2	0	0
Nebivolol	β_1*	0	0
Penbutolol	β_1 - β_2	0	+
Pindolol	β_1 - β_2	+	++
Propranolol	β_1 - β_2	++	0
Sotalol	β_1 - β_2	0	0
Timolol	β_1 - β_2	0	0

0=none; +=low; ++=moderate; +++ =high
*Inhibits β2 receptors (bronchial and vascular) at higher doses.
†Detectable only at doses much greater than required for β blockade.

Indications

Table 3: Indications[1-26]

Indication	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Angina Pectoris															
Long-term maintenance treatment								a	a						
To decrease angina frequency and increase exercise tolerance due to coronary atherosclerosis		a											a *		
Cardiac Arrhythmias															
Documented ventricular arrhythmias that in the judgement of the physician are life-threatening														a §	
Intraoperative and Postoperative Tachycardia and/or Hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia and in the postoperative period						a									
Maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter who are currently in sinus rhythm														a ‖	
Management of ventricular premature beats	a														
Persistent premature ventricular extrasystoles that impair the well-being of the patient and do not respond to conventional measures													a †		
Short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate													a †		
Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia, short term control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other emergent circumstances						a									
To abolish tachyarrhythmias due to excessive catecholamine action during anesthesia when other measures fail													a †		

To control ventricular rate in patients with atrial fibrillation and a rapid ventricular response													a ‡		
To control ventricular rate in life-threatening digitalis-induced arrhythmias													a †		
Hypertension															
Essential hypertension, alone or in combination with other antihypertensives					a										
Hypertension alone or in combination with other antihypertensives	a	a	a	a			a ‡	a	a	a		a	a		a
Hypertension, control of blood pressure in severe hypertension							a †								
Mild to moderate arterial hypertension alone or in combination with other antihypertensives											a				
Heart Failure															
Mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and, also, to reduce the risk of hospitalizations					a										
Stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin								a #							
Hypertrophic Subaortic Stenosis															
Improves NYHA functional class in symptomatic patients with hypertropic subaortic stenosis													a *		
Myocardial Infarction															
Hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality		a						a *							
Reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤40% (with or without symptomatic heart failure)					a										
Reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable													a ‡		
Reduce cardiovascular mortality and reinfarction in patients who have survived the acute phase of myocardial infarction and are clinically stable															a
Other															
Adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors													a ‡		
Familial or hereditary essential tremor													a ‡		

Treatment of proliferating infantile hemangioma requiring systemic therapy													a **		
Prophylaxis of migraine headache													a *		a

NYHA=New York Heart Association
*Indication related to controlled release 24-hour capsule formulation only
†Indication related to solution for injection formulation
‡Indication related to tablet formulation
§Indication related to tablet (Betapace) and oral solution formulations
‖Indication related to tablet (Betapace AF) and oral solution formulations
¶Indication related to oral formulations only
#Indication related to oral extended-release tablet
**Indication related to oral solution formulation

Pharmacokinetics

Table 4: Pharmacokinetics[1-26,62]

Generic Name(s)	Bio-availability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)	Lipid Solubility
Single Entity Agents						
Acebutolol	40	26	Liver	Renal (30 to 40) Bile (3 to 8) Feces (56)	3 to 4	Low
Atenolol	50	16	Not reported	Renal (40 to 50) Feces (50)	6 to 7	Low
Betaxolol	84 to 93	50	Liver, extensive (% not reported)	Renal (>80)	14 to 22	Low
Bisoprolol	80	30	Liver (50)	Renal (50) Feces (<2)	9 to 12	Low
Carvedilol	21 to 35	98	Liver, extensive (% not reported)	Renal (16) Feces (60)	6 to 10	Moderate
Esmolol	Not Reported	55	Blood Based (% not reported)	Renal (73 to 88)	9	Low
Labetalol	25	50	Liver, extensive (% not reported)	Renal (55 to 60) Feces (50)	5 to 8	Moderate
Metoprolol	50 to 77	12	Liver, extensive (% not reported)	Renal (95)	3 to 7	Moderate
Nadolol	20 to 40	28 to 30	None	Renal (25) Feces (77)	20 to 24	Low
Nebivolol	12 to 96	98	Liver, extensive (% not reported)	Renal (<1) Feces (13 to 44)	12 to 19	High
Penbutolol	100	80 to 98	Liver, extensive (% not reported)	Renal (90)	17 to 26	High
Pindolol	87 to 90	40 to 60	Liver (60 to 65)	Renal (35 to 40) Feces (6 to 9)	3 to 4	Moderate
Propranolol	30 to 70	93	Liver (50 to 70)	Renal (<1)	3 to 4	High
Sotalol	60 to 100	0	Liver, minor	Renal (66 to 75)	7 to 18	Low
Timolol	61	<10	Liver (80)	Renal (20)	2 to 4	Low-Moderate

Clinical Trials

Despite the extensive experience with β-blockers in clinical practice, there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with an arrhythmia, hypertension, or angina pectoris and other indications.[63-185]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Angina				
Pandhi et al[64] Acebutolol 100 to 400 mg TID vs propranolol 40 to 160 mg TID vs placebo	DB, XO Patients with classical anginal symptoms of effort with ≥7 attacks per week and angina being stable for ≥8 to 12 weeks	N=24 18 weeks	Primary: Incidence of anginal attack, number of nitroglycerin tablets used, exercise tolerance, side effects Secondary: Not reported	Primary: Both acebutolol and propranolol significantly reduced the incidence of anginal attacks per week compared to placebo (P<0.001 for both groups), but the difference between the two groups was not significant (P>0.05). Both acebutolol and propranolol significantly reduced the number of nitroglycerin tablets used per week compared to placebo (P<0.001 for both groups), but the difference between the two groups was not significant (P>0.05). Both acebutolol and propranolol significantly improved exercise tolerance compared to placebo (P<0.001), but the difference between the two groups was not significant (P>0.05). Side effects reported (i.e., insomnia, sweating, bitter taste, heart burn, muscle weakness) were similar between the two treatment groups. Clinical significance of the side effects was not reported. Secondary: Not reported
Jackson et al[65] Atenolol 25, 50, 100, and 200 mg/day, each dose administered for a 2 week period vs placebo All patients received SB	XO Adult patients with clinically stable exercise-induced angina for ≥3 months	N=10 12 weeks	Primary: Anginal attack rate, nitroglycerin consumption, exercise data Secondary: Not reported	Primary: Compared to placebo, atenolol reduced the angina attack rate during all periods (P<0.001). A dose response was present with a decreasing number of attacks with increasing dosage. Doses of 100 and 200 mg were significantly more effective to 25 mg (P<0.001 for both), but there was no significant difference between the 50 and 100 mg, or 100 and 200 mg (P values not reported). Nitroglycerin consumption declined in a parallel, dose-related fashion. Compared to placebo, all doses of atenolol decreased nitroglycerin consumption significantly (P<0.001), with no significant difference between 50 vs 100 and 200 mg, or 100 vs 200 mg (P values not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo for the first 4 weeks of the trial.				reported). All doses of atenolol significantly reduced resting and exercise heart rate at three hours (P<0.001) and 24 hours (P<0.001) after ingestion. Atenolol was significantly more effective at 100 and 200 mg, with no significant difference between the two doses (P value not reported). The maximal exercise double product (heart rate times SBP) at the occurrence of chest pain was significantly reduced at peak and trough testing with all atenolol doses (P<0.001 for all), but 100 and 200 mg were significantly more effective than 25 and 50 mg (P<0.001 for both). The amount of exercise necessary to produce angina three hours after drug ingestion was increased by all atenolol doses; however, only 50 (P<0.001), 100 (P<0.005) and 200 mg (P<0.001) showed significant improvement compared to placebo. Secondary: Not reported
Kardas et al[66] Betaxolol 20 mg QD vs metoprolol 50 mg BID	OL, PG, RCT Patients 40 to 75 years with ischemic heart disease NYHA class I to II, no prior β-blocker treatment, and whose mental state enabled conscious participation in the study	N=112 8 weeks	Primary: Overall compliance Secondary: Drug effectiveness, health-related QOL	Primary: The overall compliance significantly higher in the betaxolol group compared to the metoprolol group (86.5±21.3 vs 76.1±26.3%, respectively; P=0.002). Secondary: There was not a significant difference in chest pain episodes observed between the betaxolol and metoprolol groups compared from baseline (0.42/week and 0.46/week change in episodes, respectively; P>0.05). Overall, QOL dimensions were similar among both treatment groups, with the exception of physical function in which a significantly greater improvement was observed in the betaxolol group compared to the metoprolol group (42.9 vs 15.2 patients improved, respectively; P<0.01).
van der Does et al[67] Carvedilol 25 to 50 mg BID	DB, MC, RCT Patients ≤80	N=368 3 months	Primary: Moderate anginal pain and	Primary: Compared to baseline, both carvedilol and metoprolol significantly decreased time to anginal pain during exercise test (+77s [+20 to +140]

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs metoprolol 50 to 100 mg BID	years of age with CHD and chronic stable angina for ≥2 months, exertional angina with symptoms improving after taking short acting nitrates or after a period of rest, and 1 exercise test performed that was limited by moderate anginal pain		time to ST- 1-mm segment depression Secondary: Not reported	and +76 [+25 to +155], respectively; P<0.001 for both). Compared to baseline, both carvedilol and metoprolol significantly decreased time to ST- 1-mm segment depression during exercise test (+75.5 s [+47 to +154 s] and +60 [0 to +146 s], respectively; P<0.001 for both). Carvedilol significantly improved the time to 1-mm ST-segment depression compared to metoprolol (RR, 1.386; 95% CI, 1.045 to 1.839; P<0.05) Secondary: Not reported
Weiss et al[68] Carvedilol 12.5 to 50 mg BID vs placebo	DB, MC, XO Patients with 2 stress tests which evoked ischemic signs and symptoms	N=122 12 weeks	Primary: Efficacy, safety Secondary: Not reported	Primary: The carvedilol 25 and 50 mg groups significantly reduced the time to angina compared to placebo (25 mg: 337 s, P=0.0039; 50 mg: 345 s; P<0.001 vs 316 s). The carvedilol 25 and 50 mg groups significantly reduced the time to 1-mm ST-segment depression compared to placebo (25 mg: 313 s; 50 mg: 323 s vs 301 s; P<0.0001 for both). The percentage of patients reporting any adverse experience was slightly less in those receiving placebo (placebo: 28.4%; 12.5 mg: 33.1%; 25 mg: 34.5%; 50 mg: 31.9%). Adverse events included dizziness, fatigue, headache, dyspepsia, and any hypotensive event. The clinical significance of the adverse events was not reported. Secondary: Not reported
Hauf-Zachariou et al[69]	DB, MC, PG, RCT	N=313	Primary: Total exercise	Primary: There was not a significant difference in total exercise time observed

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Carvedilol 25 mg BID vs verapamil 120 mg TID	Patients 18 to 75 years with a confirmed diagnosis of CAD, exertional chest pain relieved by rest or glyceryl trinitrate for ≥2 months and 2 exercise tests with signs and symptoms of ischemia	12 weeks	time, time to onset of angina, and time to 1 mm ST-segment depression, blood pressure, heart rate, rate pressure product Secondary: Not reported	between the carvedilol (increased from 378 s to 436 s) and verapamil (increased from 386 s to 438 s) groups (RR, 1.14; 90% CI, 0.85±1.52). There was not a significant difference observed between the carvedilol and verapamil groups in time to onset of angina (increase from 296 s to 325 s vs 285 s to 326 s) and in time to 1 mm ST-segment depression (increase from 267 s to 298 s vs 286 s to 302 s). At peak exercise and at maximum comparable workload, carvedilol significantly reduced SBP (from 175 to 166 mm Hg) compared to verapamil (from 173 to 173 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced heart rate (from 123 to 112 mm Hg) compared to verapamil (from 124 to 120 mm Hg)). At peak exercise and at maximum comparable workload, carvedilol significantly reduced rate pressure product (from 21564 to 18802 mm Hg) compared to verapamil (from 21488 to 20992 mm Hg)). Secondary: Not reported
Savanitto et al[70] Weeks 1 to 6: Metoprolol ER 200 mg QD vs nifedipine 20 mg BID Weeks 7 to 10: Metoprolol ER 200 mg QD plus placebo	DB, MC, RCT Patients with typical anginal symptoms that had been stable for approximately 6 months, who showed a positive response to exercise stress	N=280 6 weeks	Primary: Angina frequency, exercise tolerance, safety Secondary: Not reported	Primary: At week six, both metoprolol (mean change, -1.95; 95 % CI, -1.25 to -2.64) and nifedipine (mean change, -1.57; 95 % CI, -0.69 to -2.45) significantly reduced the frequency of angina compared to baseline, but there was not a statistical difference between groups. At the end of 10 weeks, there was not a statistical difference observed between the groups. At week six, both metoprolol and nifedipine significantly increased the mean exercise time to l-mm ST-segment depression compared to baseline (both P<0.01); but metoprolol was significantly more effective than nifedipine (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs metoprolol ER 200 mg QD and nifedipine 20 mg BID vs nifedipine 20 mg BID plus placebo	testing with 23 min of exercise tolerance and were in sinus rhythm and had an analyzable ST segment on ECG			At week 10, the groups randomized to combination therapy had a further increase in time to l-mm ST-segment depression (P<0.05 vs placebo). There were 14 cardiovascular events including one sudden death, three acute myocardial infarctions, eight cases of unstable angina, one of syncope and one of stroke and the incidence of these events did not differ among the treatment groups. Secondary: Not reported
Turner et al[71] Propranolol 40 to 240 mg/day, administered in 4 divided doses vs nadolol 40 to 240 mg/day, administered in 2 divided doses vs placebo	DB, PC, RCT, XO Men with ischemic heart disease with presence of stable angina pectoris and absence of acute MI during the preceding 4 months, ECG evidence of myocardial ischemia during treadmill exercise testing and/or arteriographic evidence of >60% obstruction of the lumen of ≥2	N=14 Up to 18 weeks	Primary: Glyceryl trinitrate consumption, exercise tolerance, heart rate Secondary: Not reported	Primary: Mean glyceryl trinitrate consumption decreased significantly from placebo with both propranolol and nadolol (P<0.05 for all). There was no significant difference between propranolol and nadolol, with nadolol 240 mg/day producing a significant decrease in consumption of glyceryl trinitrate compared to 160 mg/day (P<0.05). Both treatments resulted in similar improvements in exercise tolerance (30%; P<0.01) and external work performed (48%; P<0.01). A slightly greater suppression of heart rate during exercise was observed with nadolol compared to propranolol (P<0.05). Both treatments resulted in significant decreases in resting heart rate; however, the rate corrected systolic time intervals changed very little from control. The effects of the two treatments could not be differentiated by echocardiography or phonocardiography. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	major coronary arteries, the absence of CHF, a resting DBP <90 mm Hg, absence of contra-indications to β-blocker therapy and the absence of other cardiac or severe systemic disease			
Arrhythmias				
Lui et al[72] Acebutolol 200 or 400 mg/day vs placebo	DB, PC, RCT, XO Adult patients with ≥30 ventricular ectopic beats per hour on 3 control ambulatory monitoring	N=25 Not reported	Primary: Resting heart rate, ventricular arrhythmias, paired ventricular ectopic beats, ventricular tachycardia, electro-physiologic effects, adverse events Secondary: Not reported	Primary: Both doses of acebutolol produced a significant decrease in heart rate (P<0.01 for both), with no significant differences between 200 and 400 mg (P value not reported). Mean ventricular ectopic beat reduction from the control period was 34.9% during the two placebo periods. Following acebutolol, mean ectopic beat suppression was greater, although not significantly different when compared to placebo, at 44.9 and 49.5% using 200 and 400 mg, respectively (P values not reported). Nineteen of the 25 patients achieved episodes of paired ventricular ectopic beats (couplets) on control ambulatory monitoring. The mean reduction of paired beats was significantly higher than placebo (48.8%) with 70.5 (P<0.05) and 74.5% (P<0.01) with acebutolol 200 and 400 mg, respectively. Five patients who had ventricular tachycardia during both control and placebo periods had complete suppression during acebutolol treatment. Mean QRS and QTc intervals revealed no significant difference as

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to the control period. There were no significant adverse effects related to acebutolol administration. Patients did not develop any bronchospasm, significant bradycardia, heart block, CHF or any central nervous system adverse effect. Secondary: Not reported
Lee et al[73] Amiodarone vs sotalol vs β-blockers (agents not specified) Doses of the agents were not specified	RETRO Patients with AF and/or CHF (NYHA class ≥III) and an implantable cardioverter defibrillator	N=55 2.6 years	Primary: Cumulative rates of inappropriate shocks Secondary: Not reported	Primary: Amiodarone demonstrated a significantly lower rate of inappropriate shock was compared β-blocker group (27.3 vs 70.6% at four years; P=0.003). This demonstrated an 83% reduction compared to the β-blockers (HR, 0.17; 95% CI, 0.05 to 0.64; P=0.008). There was not a significant difference in rates of inappropriate shocks observed between the amiodarone and sotalol groups (27.3 vs 54.3% at four years; P=0.29). There was not a significant difference in rates of inappropriate shocks observed between the sotalol and β-blocker groups (54.3 vs 70.6% at four years; P=0.16). Secondary: Not reported
Connolly et al[74] OPTIC β-blocker (bisoprolol, carvedilol or metoprolol) vs sotalol 240 mg/day in two to three divided doses	DB, MC, RCT Patients who received an implantable cardioverter defibrillator within 21 days of randomization, had sustained	N=412 12 months	Primary: Implantable cardioverter defibrillator shock for any reason Secondary: Not reported	Primary: Shocks occurred in 41 patients (38.5%) in the β-blocker group, 26 (24.3%) in the sotalol group, and 12 (10.3%) in the amiodarone plus β-blocker group. A reduction in the risk of shock was observed with use of amiodarone plus β-blocker or sotalol vs β-blocker alone (HR, 0.44; 95% CI, 0.28 to 0.68; P<0.001). The amiodarone plus β-blocker group significantly reduced the risk of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amiodarone 200 mg QD plus β-blocker (bisoprolol, carvedilol or metoprolol) Amiodarone was loaded at 400 mg BID for 2 weeks, followed by 400 mg/day for 4 weeks, and then 200 mg/day until then end of the study	ventricular tachycardia, ventricular fibrillation or cardiac arrest, LVEF ≤40%, inducible ventricular tachycardia or ventricular fibrillation by programmed ventricular stimulation with LVEF ≤40% or unexplained syncope with ventricular tachycardia or ventricular fibrillation, inducible by programmed stimulation			shock compared to β-blocker alone (HR, 0.27; 95% CI, 0.14 to 0.52; P<0.001) and sotalol (HR, 0.43; 95% CI, 0.22 to 0.85; P=0.02). Sotalol did not significantly reduce the risk of shock compared to the β-blocker alone group (HR, 0.61; 95% CI, 0.37 to 1.01; P=0.055). Secondary: Not reported
Balcetyte-Harris et al[75] Esmolol 0.5 mg/kg over 5 minutes then 0.05 mg/kg/min titrated to heart rate of 55 to 65 bpm and SBP >100 mm Hg for up to 24 hours vs	OL, RCT Patients referred for elective CABG without concomitant valve replacement who were in sinus rhythm	N=50 72 hours	Primary: Development of AF lasting >30 mins Secondary: Development of adverse events, hypotension (SBP <90 mm Hg),	Primary: There was not a significant difference in development of AF after CABG between the esmolol and β-blocker group (seven [26%] vs six [26%] patients, respectively). Secondary: Significantly more patients in the esmolol group experienced significant adverse events compared to the patients in the β-blocker group (11 [41%] vs one [4%] patient(s), respectively; P=0.006). Significantly more patients in the esmolol group experienced

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oral β-blocker (metoprolol ≥50 mg/day was the preferred agent)			symptomatic bradycardia or CHF (left ventricular failure)	hypotension compared to the patients in the β-blocker group (eight vs one patient(s), respectively; P=0.03). There was not a statistically significant difference between the esmolol and the β-blocker group in the development bradycardia requiring pacing (two vs zero patients, respectively) and in left ventricular failure (one vs zero patient(s), respectively).
Kettering et al[76] Metoprolol 25 to 200 mg/day vs sotalol 40 to 480 mg/day	PRO, RCT Symptomatic patients between 18 and 80 years with sustained ventricular tachycardia and/or ventricular fibrillation requiring an implantable cardioverter defibrillator	N=100 2 years	Primary: Ventricular tachycardia or ventricular fibrillation recurrence requiring implantable cardioverter defibrillator intervention Secondary: Total mortality	Primary: There was not a significant difference in ventricular tachycardia/ ventricular fibrillation recurrence rates observed between the metoprolol group (33 patients) and the sotalol group (30 patients; P=0.68). After one year of treatment, 46.3% of patients in the metoprolol group and 54.7% of patients in the sotalol group were free of a recurrence of ventricular tachycardia or ventricular fibrillation (P=0.68). After two years, rates were 31.5 and 36.6%, respectively. Secondary: There was not a significant difference in mortality rates observed between the metoprolol group (eight deaths) and the sotalol group (six patients; P=0.43).
Seidl et al[77] Metoprolol 50 mg/day vs sotalol 80 mg/day The doses of the study medications were titrated to the maximum titrates dose.	OL, RCT Patients >18 years of age requiring treatment if life-threatening ventricular tachycardia/ ventricular fibrillation who required an implantable	N=70 26±16 months	Primary: Recurrence of ventricular tachycardia requiring antitachycardia pacing, fast ventricular tachycardia or ventricular fibrillation requiring implantable	Primary: Actuarial rates for absence of ventricular tachycardia recurrence were significantly higher in the metoprolol group vs the sotalol group at one and two years (83 and 80 vs 57 and 51%, respectively; P=0.016). Actuarial rates for absence of recurrence of a fast ventricular tachycardia or ventricular fibrillation were significantly higher in the metoprolol group vs the sotalol group one and two years (88 and 80 vs 54 and 46%, respectively; P=0.002) Actuarial survival rates at one and two years were not significantly different between the metoprolol and sotalol groups (94 and 91 vs 86 and 83%, respectively; P=0.287)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	cardioverter defibrillator due to non-inducible or drug refractory (≥1 unsuccessful antiarrhythmic trial) arrhythmias		cardioverter defibrillator, discharges, total mortality Secondary: Not reported	Secondary: Not reported
Steeds et al[78] Sotalol 80 mg BID vs atenolol 50 mg QD	OL, PRO, RCT, XO Symptomatic patients >50 years of age with paroxysmal AF documented on ECG	N=47 2 months	Primary: Frequency of paroxysmal AF Secondary: Average and total duration of paroxysmal AF, total ectopic count, symptom assessments	Primary: There was not a significant difference in frequency of episodes of paroxysmal AF observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1; P=0.47). Secondary: There was not a significant difference in average duration of episodes of paroxysmal AF observed between the sotalol and atenolol groups (median difference, 0 min; 95% CI, 0 to 1 min; P=0.31) or in total duration of episodes of paroxysmal AF (median difference, 0 min; 95% CI, -1 to 2 min; P=0.51). There was not a significant difference in total ectopic count observed between the sotalol and atenolol groups (median difference, -123; 95% CI, -362 to 135; P=0.14) during either treatment period. There was not a significant difference in tolerance and symptom scores observed between the sotalol and atenolol groups (median difference, -5; 95% CI, -20 to 5; P=0.26)
Essential Tremor				
Calzetti et al[79] Metoprolol 150 mg/dose vs	DB, PC, RCT Patients 19 to 72 years with essential tremor and symptomatic	N=23 3 weeks	Primary: Tremor magnitude, heart rate, blood pressure	Primary: Both metoprolol (47±9.7%) and propranolol (55±5.0%) significantly decreased tremor magnitude from baseline compared to placebo (22±7.3%; P<0.01 for both treatments compared to placebo), but there was not a significant difference observed between the metoprolol and propranolol groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
propranolol 120 mg/dose vs placebo	for ≥1 year prior to the study		Secondary: Not reported	Both propranolol (0.073) and metoprolol (0.01) significantly diminished the normal increase in pulse rate on standing (P<0.01) and placebo had no effect on such pulse rate. There was not a significant difference observed between the metoprolol and propranolol groups. Both metoprolol and propranolol significantly reduced the SBP from baseline compared to placebo, in the supine and standing positions (P<0.05). Secondary: Not reported
Yetimalar et al[80] Propranolol 120 mg/day vs olanzapine 20 mg/day	DB, RCT, XO Patients with essential tremor and previous therapy with ≥1 medications for essential tremor without significant benefit, which was withdrawn ≥1 month before study drug was given	N=38 74 days	Primary: Tremor, global QOL Secondary: Not reported	Primary: After 30 days, both propranolol and olanzapine significantly reduced the all tremor evaluation measures (i.e., speaking, eating, dressing, writing working) compared to baseline (P=0.000), but at the end of the study, olanzapine significantly improved all tremor evaluation measures (P<0.05) except hygiene (P =0.08) as compared to propranolol. Both propranolol (63%) and olanzapine (87%) significantly improved global QOL from baseline, but olanzapine significantly improved the global QOL score compared to propranolol (4.5±0.7 vs 3.6±0.9; P=0.000). Secondary: Not reported
Gironell et al[81] Propranolol 40 mg TID vs gabapentin 400 mg TID	DB, PC, XO Patients with moderate to severe essential tremor that was chronic (≥5 years),	N=16 66 days	Primary: Tremor Clinical Rating Scale, accelerometric recordings, self-reported disability scale	Primary: Both gabapentin and propranolol significantly reduced the clinical examination and motor task performance components of the Tremor Clinical Rating Scale compared to placebo (-3.10±1.10; P=0.01 and -4.50±1.10; P=0.001, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.40±1.16; P=0.23).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	persistent, and bilateral postural tremor with or without kinetic tremor involving hands or forearms, with no other neurological abnormalities or explanation for tremor		Secondary: Not reported	Both gabapentin and propranolol significantly reduced the activities of daily living component of the Tremor Clinical Rating Scale compared to placebo (-3.03±1.46; P<0.05 and -4.95±1.46; P=0.002, respectively), and significant differences were not observed between the gabapentin and propranolol groups (1.92±1.46; P=0.20). Both gabapentin and propranolol significantly reduced the patient's subjective assessment of the Tremor Clinical Rating Scale compared to placebo (1.37±0.46; P=0.006 and 1.44±0.46; P=0.004, respectively). Significant differences were not observed between the gabapentin and the propranolol groups (-0.07±0.46; P=0.89). Both gabapentin and propranolol significantly reduced the absolute power of the dominant frequency peak of accelerometry compared to placebo (-2352.0±1153.3; P=0.05 and -2282.14±1116.58; P=0.05, respectively), but significant differences were not observed between the gabapentin and the propranolol groups (-70.39±1165.22; P=0.95. Gabapentin significantly reduced the self-reported disability scale score more than placebo (-6.04±2.75; P=0.04) and propranolol did not (-4.48±2.75; P=0.11), but there were no significant differences between the gabapentin and propranolol groups (-1.55±2.75; P=0.58). Secondary: Not reported
Heart Failure				
CIBIS Investigators and Committees[82] CIBIS Bisoprolol 1.25 to 5 mg QD vs	DB, MC, PC, PG, RCT Patients 18 to 75 years with NYHA functional class III or IV due to idiopathic dilated	N=641 1.9 years	Primary: Total mortality Secondary: Tolerability, analysis critical events	Primary: There was no statistical significance between bisoprolol and placebo in total mortality (53 vs 67; RR, 0.80; 95% CI, 0.56 to 1.15; P=0.22). Secondary: Bisoprolol was well tolerated with no between group difference in premature treatment withdrawals (82 on placebo, 75 on bisoprolol; not significant).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patient received standard therapy (diuretic and vasodilator)	cardiomyopathy, ischemia, HTN or valvular heart disease, a LVEF of <40%, and background therapy with a diuretic and a vasodilator			Significantly fewer patients in the bisoprolol group required hospitalization for cardiac decompensation (90 in placebo versus 61 in bisoprolol; P<0.01), and more patients improved by at least one NYHA functional class (48 on placebo versus 68 on bisoprolol; P=0.04) by the end of follow-up period.
CIBIS-II Investigators and Committees[83] CIBIS-II Bisoprolol 1.25 to 10 mg QD added to usual therapy (diuretic and vasodilator) vs placebo	DB, MC, PC, RCT Symptomatic patients 18 to 80 years in NYHA class III or IV, with LVEF of 35% or less receiving standard therapy with diuretics and ACE inhibitor or other vasodilator	N=2,647 1.3 years	Primary: All-cause mortality Secondary: All-cause hospital admissions, cardiovascular mortality, cardiovascular mortality and cardiovascular hospital admissions (composite endpoint), permanent premature treatment withdrawals	Primary: CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than on placebo (156 [11.8%] vs 228 [17.3%] deaths, respectively; HR, 0.66; 95% CI, 0.54 to 0.81; P<0.0001). Significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs 83 [6.3%] deaths, respectively; HR, 0.56; 95% CI, 0.39 to 0.80; P=0.0011). Secondary: All-cause hospital admissions was significantly lower with bisoprolol than on placebo (440 [33%] vs 513 [39%] patients, respectively; HR, 0.80; 95% CI, 0.71 to 0.91; P=0.0006). All-cardiovascular deaths was significantly lower with bisoprolol than on placebo (119 [9%] vs 161 [12%] patients, respectively; HR, 0.71; 95% CI, 0.56 to 0.90; P=0.0049). Occurrence of composite endpoints of all cardiovascular deaths and cardiovascular admissions was significantly lower with bisoprolol than on placebo (388 [29%] vs 463 [35%] patients, respectively; HR, 0.79; 95% CI, 0.69 to 0.90; P=0.0004). Occurrence of treatment withdrawals was not statistically different

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				between bisoprolol and the placebo group (194 [15%] vs 192 [15%] patients, respectively; HR, 1.00; 95% CI, 0.82 to 1.22; P=0.98).
Contini et al[84] CARNEBI Bisoprolol vs carvedilol vs nebivolol each at maximal clinically tolerated dose	RCT, XO Patients aged 18 to 80 years with diagnosis of either idiopathic or ischemic dilated cardiomyopathy, previous evidence of LVEF ≤ 40%, NYHA class I to III with stable clinical conditions and optimized drug regimen	N=61 Each patient performed a 2-month therapy with each β-blocker	Primary: Clinical conditions, quality of life, laboratory data, echocardiographic evaluation, spirometry, alveolar capillary membrane diffusion, chemoreceptor response, cardiopulmonary exercise test, and response to hypoxia during constant workload exercise Secondary: Not reported	Primary: Clinical conditions, NYHA class, Minnesota questionnaire, renal function, hemoglobin concentration, brain natriuretic peptide, Echocardiographic data, and Doppler data were unaffected by the different β-blockers studied. Carbon monoxide diffusing capacity was lower on Carvedilol (18.3 ± 4.8* mL/min/mm Hg) compared to Nebivolol (19.9 ± 5.1) and Bisoprolol (20.0 ± 5.0) due to membrane diffusion 20% reduction (*= P< 0.0001). Constant workload exercise showed in hypoxia a faster VO_2 (oxygen uptake) kinetic and a lower ventilation with Carvedilol. Peripheral and central sensitivity to CO_2 was lower in Carvedilol while response to hypoxia was higher in Bisoprolol. Secondary: Not reported
Willenheimer et al[85] CIBIS-III Bisoprolol 1.25 to 10 mg QD vs enalapril 2.5 to 10 mg BID	BE, MC, OL, PG, RCT Patients ≥65 years with stable mild to moderate CHF (NYHA class II to III), LVEF of ≤35% ≥3 months prior	N=1,010 1.22±0.42 years	Primary: Combined all-cause mortality or hospitalization Secondary: Combined end point at the end of the monotherapy	Primary: There were 178 patients (35.2%) with a primary end point of combined all-cause mortality or all-cause hospitalization in the bisoprolol-first group, compared to 186 (36.8%) patients in the enalapril-first group (absolute difference, -1.6%; 95% CI, -7.6 to 4.4; HR, 0.94; 95% CI, 0.77 to 1.16; non-inferiority for bisoprolol-first vs enalapril-first treatment; P=0.019). Secondary: The combined endpoint at the end of the monotherapy phase occurred

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	to randomization, not on an ACE inhibitor, β-blocker or ARB therapy and no clinically relevant fluid retention of diuretic adjustment within the 7 days prior to randomization		phase and the individual components of the primary end point, cardiovascular death and cardiovascular hospitalization, permanent treatment cessation and the need for early introduction of the second drug as indicators of drug tolerability	in 109 patients in the bisoprolol-first group compared to 108 patients in the enalapril-first group (HR, 1.02; 95% CI, 0.78 to 1.33; between-group difference P=0.90); 23 vs 32 patients died, respectively (HR, 0.72; 95% CI, 0.42 to 1.24; between-group difference P=0.24); and 99 vs 92 patients had been a hospitalization, respectively (HR, 1.08; 95% CI, 0.81 to 1.43; between-group difference P=0.59). There were 65 deaths in the bisoprolol-first group, as compared to 73 in the enalapril-first group (HR, 0.88; 95% CI, 0.63 to 1.22; between-group difference P=0.44). In the bisoprolol-first group, 151 patients were hospitalized, compared to 157 patients in the enalapril-first group (HR, 0.95; 95% CI, 0.76 to 1.19; between-group difference P=0.66). There was not a significant difference in cardiovascular death rate observed between the bisoprolol-first (55) and enalapril-first (56) treatment groups (HR, 0.97; 95% CI, 0.67 to 1.40; between-group difference P=0.86). During the monotherapy phase, 35 (6.9%) patients in the bisoprolol-first group permanently discontinued therapy, compared to 49 (9.7%) patients in the enalapril-first group. During the combined-therapy phase, 19 patients (4.2%) in the bisoprolol-first group permanently discontinued bisoprolol therapy and 47 (10.4%) discontinued enalapril therapy. In the enalapril-first group, 24 patients (5.5%) permanently discontinued bisoprolol and 16 (3.7%) discontinued enalapril. There was not a statistical significant difference observed in the early introduction of the second drug between the bisoprolol-first group (39 [7.7%] patients) compared to the enalapril-first group (37 [7.3%] patients; P=0.81).
Packer et al[86] COPERNICUS	DB, MC, PC, RCT	N=2,280 10.4 months	Primary: Total mortality	Primary: The study was stopped early due to statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Carvedilol 3.125 to 25 mg BID vs placebo	Patients with severe chronic heart failure as a result of ischemic or nonischemic cardiomyopathy, dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% despite appropriate conventional therapy with diuretics, and an ACE inhibitor, or ARB		Secondary: Combined risk of death or hospitalization for any reason, withdrawal rates	The annual mortality in the placebo group was 19.7% (190) versus 12.8% (130 deaths) in the carvedilol group, a 35% reduction in mortality (95% CI, 19 to 48%; P<0.00013). Secondary: Carvedilol reduced the combined risk of death or hospitalization for any reason by 24% compared to placebo (425 vs 507 patients; 95% CI, 13 to 33%; P<0.001) Withdrawal rates were significantly higher in the placebo group compared to the carvedilol group (18.5 vs 14.8; P=0.02).
Packer et al[87] COPERNICUS Carvedilol 3.125 mg BID, titrated up to 25 mg BID vs placebo	DB, PC, RCT Patients with dyspnea or fatigue at rest or on minimal exertion for ≥2 months and a LVEF <25% as a result of an ischemic or nonischemic cardiomyopathy, being treated with a diuretic	N=2,289 10.4 months	Primary: All-cause mortality Secondary: Combined risk of death or hospitalization for any reason, combined risk of death or hospitalization for any cardiovascular reason,	Primary: The annual mortality rate with placebo was 19.7% per patient year of follow up, which was reduced to 12.8% by treatment with carvedilol, corresponding to a 35% reduction in the risk of death (P=0.00013). Secondary: Carvedilol reduced the risk of death or any hospitalization by 24% (P=0.00004). Carvedilol reduced the combined risk of death or hospitalization for cardiovascular reason by 27% (P=0.0002) and the combined risk of death or hospitalization for heart failure by 31% (P=0.000004). Patients receiving carvedilol spent 27% fewer days in the hospital for any reason (P=0.005) and 40% fewer days in the hospital for heart

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and either an ACE inhibitor or ARB		combined risk of death or hospitalization for heart failure, patient global assessment	failure (P<0.0001). More patients receiving carvedilol felt improved and fewer patients felt worse compared to patients receiving placebo after six months of maintenance therapy (P=0.0009). Patients receiving carvedilol were less likely to experience a serious adverse event (P=0.002), especially worsening heart failure, sudden death, cardiogenic shock or ventricular tachycardia.
Packer et al[88] Carvedilol 3.125 mg BID, titrated up to 50 mg BID vs placebo	DB, PC, RCT Patients with symptoms of heart failure for ≥3 months and an ejection fraction ≤35%, despite ≥2 months of treatment with diuretics and an ACE inhibitor (if tolerated)	N=1,094 6 to 12 months	Primary: All-cause mortality, cardiovascular morbidity Secondary: Not reported	Primary: Thirty one (7.8%) patients receiving placebo died compared to 22 (3.2%) deaths in patients receiving carvedilol; this difference represents a 65% decrease in the risk of death (95% CI, 39 to 80; P<0.001). Treatment with carvedilol was associated with a large decrease in the risk of dying of progressive heart failure and in the risk of sudden death. Ninety eight (14.1%) patients receiving carvedilol and 78 patients (19.6%) receiving placebo had at least one hospitalization for cardiovascular causes; this difference represents a 27% reduction in the risk of hospitalization (95% CI, 3 to 45; P=0.036). Secondary: Not reported
Dargie et al[89] CAPRICORN Carvedilol 6.25 to 25 mg BID mg vs placebo	DB, MC, PC, RCT Patients 18 years and older with a stable MI occurring 3 to 21 days prior to randomization, LVEF ≤40% and ACE inhibitor therapy for ≥48	N=1,959 1.3 years	Primary: All-cause mortality, all-cause mortality or cardiovascular hospital admissions Secondary: Sudden death, hospital	Primary: There was not a significant difference observed between the carvedilol and placebo groups in the combined endpoint of all-cause mortality and hospital admissions due to cardiovascular events (340 [35%] vs 367 [37%], respectively; HR, 0.92; 95% CI, 0.80 to 1.07; P=0.296). All-cause mortality alone was statistically better in the carvedilol group than the placebo group (116 [12%] vs 151 [15%], respectively; HR, 0.77; 95% CI, 0.60 to 0.98; P=0.031). Secondary: There was not a significant difference observed between the carvedilol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hours		admission for heart failure, recurrent nonfatal MI, all-cause mortality or recurrent nonfatal MI	and placebo groups in sudden death (51 [5%] vs 69 [7%], respectively; HR, 0.74; 95% CI, 0.51 to 1.06; P=0.098) or in hospital admissions for heart failure (118 [12%] vs 138 [14%], respectively; HR, 0.86; 95% CI, 0.67 to 1.09; P=0.215). The carvedilol group, compared to placebo, experienced significantly lower rates of nonfatal MIs (34 [3%] vs 57 [6%], respectively; HR, 0.59; 95% CI, 0.39 to 0.90; P=0.014) and all-cause mortality or recurrent nonfatal MI (139 [14%] vs 192 [20%], respectively; HR, 0.71; 95% CI, 0.57 to 0.89; P=0.002).
Krum et al (abstract)[90] Carvedilol 25 mg BID vs placebo	DB, PC, RCT Patients with severe chronic HF receiving digitalis, diuretics and an ACE inhibitor (if tolerated)	N=56 14 weeks	Primary: Cardiac performance; symptom score; combined risk of death, worsening heart failure, and life-threatening ventricular tachycardia Secondary: Not reported	Primary: Compared to placebo, carvedilol improved cardiac performance, as reflected by an increase of LVEF (P=0.005) and stroke volume index (P=0.010), and a decrease in pulmonary wedge pressure (P=0.003), mean right atrial pressure (P=0.002) and systemic vascular resistance (P=0.017). Compared to placebo, carvedilol improved symptom scores (P=0.002), functional class (P=0.013) and submaximal exercise tolerance (P=0.006). The combined risk of death, worsening heart failure and life-threatening ventricular tachyarrhythmia was lower with carvedilol compared to placebo (P=0.028). Carvedilol was associated with more dizziness and advanced heart block. Secondary: Not reported
Bristow et al[91] Carvedilol 6.25 mg BID vs	DB, MC, PC, RCT Symptomatic (≥3 months)	N=345 6 months	Primary: Submaximal exercise improvement	Primary: There were no differences on submaximal exercise with any dose compared to placebo. Walk distances between in each group ranged between 300 to 400 m in both the 6-minute and 9-minute walk tests; P=0.50 and P=0.27, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
carvedilol 12.5 mg BID vs carvedilol 25 mg BID vs placebo All patients remained on their standard medications.	patients, 18 to 85 years with stable heart failure from ischemic or nonischemic dilated cardiomyopathy, an LVEF of ≤35%, a 6-minute walk test between 150 to 425 m and on stable doses of diuretics and ACE inhibitors for 2 weeks before baseline testing		Secondary: Minnesota questionnaire, changes in NYHA functional class, changes in LVEF, hospitalization, changes in signs and symptoms of heart failure, occurrence of adverse clinical experiences, survival	Secondary: There were no significant changes in the overall Minnesota Questionnaire scores incorporating both physical and emotional dimensions (changes from baseline in the placebo and low-, medium-, and high-dose carvedilol groups of -7.3, -7.9, -7.3, and -6.6, respectively; P=0.512 in difference from placebo). There were no significant improvements in NYHA functional classes in the carvedilol groups compared to placebo (actual values not reported; P=0.64). Carvedilol treatment resulted in a dose-related significant improvement in LVEF; carvedilol 6.25 mg (~5 ejection fraction units; P<0.005), 12.5 mg (~6 ejection fraction units; P<0.005) and 25 mg (~7.5 ejection fraction units; P<0.0001) compared to placebo (2 ejection fraction unit improvement). The mean number of hospitalizations per patient were significantly reduced in each of the carvedilol groups (~0.1 hospitalizations) compared to placebo (~0.35; P<0.01). Bradycardia was significantly higher in the carvedilol 12.5 mg group (10 [11%]) and the 25 mg group (10 [11%]) compared to placebo (1 [1%]; P<0.05). Also, dizziness was significantly higher in the carvedilol 25 mg group (34 [38%]) compared to the placebo group (19 [23%]; P<0.05). The clinical significance of these advents was not mentioned. There was a dose-related, statistically significant reduction in mortality in the carvedilol-treated groups, with respective mortality rates of 6.0% for the carvedilol 6.25 mg group (RR, 0.356; 95% CI, 0.127 to 0.998; P<0.05), 6.7% for the 12.5 mg group (HR, 0.416; 95% CI, 0.158 to 1.097; P=0.07), and 1.1% in the 25 mg group (HR, 0.067; 95% CI, 0.009 to 0.512; P<0.001) compared to 15.5% mortality in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Combining all three carvedilol arms of the study compared to the placebo arm showed statistical significance in all-cause mortality, risk reduced by 73% (P<0.001).
Poole-Wilson et al[92] COMET Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, MC, PG, RCT Patients with NYHA class II to IV heart failure, admission for a cardiovascular reason in the previous 2 years, an LVEF of <35%, and were stable and optimized with diuretics for ≥2 weeks and ACE inhibitor for ≥4 weeks unless not tolerated	N=3,029 58 months	Primary: All-cause mortality, composite endpoint of mortality or all-cause admission Secondary: Not reported	Primary: All-cause mortality was significantly lower in the carvedilol group compared to the metoprolol group (512 [34%] vs 600 [40%], respectively; HR, 0.83; 95% CI, 0.74 to 0.93; P=0.0017). Cardiovascular deaths were significantly lower in the carvedilol group compared to the metoprolol group (438 [29%] vs 534 [35%], respectively; HR, 0.80; 95% CI, 0.70 to 0.90; P=0.0004). There was not a significant difference in the composite endpoints of all-cause mortality or all-cause admission observed between the carvedilol and metoprolol groups (1,116 [74%] vs 1,160 [76%], respectively; HR, 0.94; 95% CI, 0.86 to 1.02; P=0.122). Secondary: Not reported
Packer et al[93] Carvedilol 50 to 100 mg/day vs metoprolol 50 to 150 mg/day or metoprolol ER 150 to 200 mg/day or	MA (19 trials) Patients with NYHA class II or III and LVEF dysfunction	N=2,779 8.3 months	Primary: Change in LVEF Secondary: Not reported	Primary: In the six placebo-controlled trials, metoprolol significantly increased the mean LVEF by 0.063±0.002 compared to the increase with placebo of 0.025±0.001 (difference of 0.038±0.005; P<0.0001). In the nine placebo-controlled trials, carvedilol significantly increased the mean LVEF by 0.079±0.001 compared to the increase with placebo of 0.012±0.001 (difference of 0.065±0.005; P<0.0001). Comparing the two agents, carvedilol increased the LVEF significantly greater than metoprolol (difference of 0.026±0.007; P=0.0002). In the four direct comparator trials, carvedilol significantly increased the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				mean LVEF by 0.089±0.002 compared to the increase with metoprolol of 0.055±0.002 (difference of 0.029±0.011; P=0.009). Secondary: Not reported
Arumanayagam et al[94] Carvedilol 25 mg BID vs metoprolol 50 mg BID	DB, RCT Symptomatic Chinese patients with CHF and LVEF of <45%	N=24 12 weeks	Primary: Plasma total antioxidant status, erythrocyte superoxide dismutase and glutathione peroxidase Secondary: Not reported	Primary: Neither carvedilol nor metoprolol significantly reduced total antioxidant status activities after 12 weeks of therapy (1.65±0.06 to 1.68±0.09 and 1.44±0.05 to 1.51±0.06 mmol/L, respectively). Carvedilol significantly reduced erythrocyte superoxide dismutase activity after 12 weeks of therapy, (986±46 to 871±22 U/g Hb; P <0.001), but metoprolol did not (790±43 to 836±46 U/g Hb). Carvedilol significantly reduced glutathione peroxidase activity after 12 weeks of therapy, (145±7 to 132±9 U/g Hb; P <0.05), but metoprolol did not (143±8 to 138±9 U/g Hb). Secondary: Not reported
Sanderson et al[95] Carvedilol 25 mg BID vs metoprolol 50 mg BID All patients continued on their standard therapy.	DB, PG, RCT Symptomatic patients with CHF, LVEF of <45%, and on standard therapy (diuretics, digoxin and ACE inhibitor)	N=51 12 weeks	Primary: Symptom score (QOL questionnaire and NYHA class), exercise tolerance time, LVEF Secondary: Not reported	Primary: A significant improvement in symptom scores from baseline were experienced in both the carvedilol (17.2±3 to 8.1±2; P<0.001) and metoprolol (13.1±1.8 to 4.8±1.4; P<0.001) groups, but there was not a significant difference between the agents. A significant improvement in NYHA class from baseline were experienced in both the carvedilol (2.6±0.11 to 2.2±0.12; P<0.001) and metoprolol (2.7±0.09 to 2.1±0.09; P<0.001) groups, but there was not a significant difference between the agents. A significant improvement in exercise tolerance time from baseline were experienced in both the carvedilol (1122±51 to1194±63; P<0.05) and metoprolol (1164±46 to 1263±52; P<0.01) groups, but there was not a significant difference between the agents.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A significant improvement in LVEF from baseline were experienced in both the carvedilol (26±1.8 to 35±2.6; P<0.001) and metoprolol (25±1.8 to 31±2.5; P<0.001) groups, but there was not a significant difference between the agents. Secondary: Not reported
Lechat et al[96] β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol) vs placebo	MA (18 trials) Patients with NYHA class I to IV chronic heart failure	N=3,023 1.5 to 15 months	Primary: All-cause mortality, hospitalizations due to heart failure, combination of all-cause mortality and hospitalizations for worsened heart failure, changes in functional status, changes in LVEF Secondary: Not reported	Primary: All endpoints showed a significant effect for β-blockers (P<0.05). β-blockers demonstrated a 32% reduction in risk of death compared to placebo (130 vs 156 deaths; 95% CI, 12% to 47%; P=0.003). β-blockers demonstrated a 41% reduction in hospitalizations due to heart failure compared to placebo (166 vs 223 hospitalizations; 95% CI, 26% to 52%; P<0.001). β-blockers demonstrated a 37% reduction in the combination of mortality and morbidity compared to placebo (239 vs 293; 95% CI, 24% to 49%; P<0.001). β-blockers demonstrated a 32% increase in the likelihood of improvement in NYHA class (95% CI, 1% to 74%; P=0.04) and a 30% decrease in the likelihood of worsening NYHA (95% CI, 4% to 50%; P=0.03) compared to placebo β-blockers demonstrated a 29% increase in ejection fraction compared to placebo (0.23±0.04 vs 0.31±0.04; P<10–9). β-adrenergic agents did not differ in respect to any outcome measure except that reduction in mortality risk. Beta selective agents were less robust than the nonselective agents (P=0.049). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Brophy et al[97] β-blockers (bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol) vs placebo	MA (22 trials) Patients with CHF of various etiologies	N=10,135 3 to 23 months	Primary: Overall mortality, hospitalizations for CHF Secondary: Not reported	Primary: β-blockers significantly reduced mortality compared to placebo (444 vs 624; OR, 0.65; 95% CI, 0.53 to 0.80). β-blockers significantly reduced hospitalizations due to CHF compared to placebo (540 vs 754; RR, 0.64; 95% CI, 0.53 to 0.79). The probability that β-blocker therapy reduced total mortality and hospitalizations for congestive heart failure was almost 100%. The best estimates of these advantages are 3.8 lives saved and four fewer hospitalizations per 100 patients treated in the first year after therapy. The probability that these benefits are clinically significant (>2 lives saved or >2 fewer hospitalizations per 100 patients treated) is 99%.
Whorlow et al[98] β-blockers (bisoprolol, bucindolol, carvedilol metoprolol, nebivolol) vs placebo	MA (18 trials) Patients with NYHA class IV heart failure currently taking background therapy (ACE inhibitors and diuretics with or without digoxin)	N=8,119 3 to 21 months	Primary: Mortality in NYHA class IV patients Secondary: Not reported	Primary: β-blockers demonstrated a 29% reduction in mortality compared to placebo in patients with NYHA class IV (RR, 0.71; 95% CI, 0.52 to 0.96). The 29% risk reduction is similar to risk reduction seen with β-adrenergic blockers in other NYHA classes. β-blockers demonstrated a 32% reduction in mortality compared to placebo in patients with NYHA class I to IV (HR, 0.68; 95% CI, 0.61 to 0.77). Secondary: Not reported
Bouzamondo et al[99] β-blockers (bisoprolol, bucindolol, carvedilol, and metoprolol) vs	MA Randomized controlled evaluating patients with heart failure	N=not specified Duration varied	Primary: Overall mortality, hospitalized for worsening heart failure Secondary:	Primary: β-blockers reduced overall mortality by 22% compared to placebo (95% CI, 16% to 28%). β-blockers reduced hospitalizations due to worsening heart failure by 24% compared to placebo (95% CI, 20% to 29%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	depending on NYHA class		Not reported	Benefits were similar for bisoprolol, metoprolol, and carvedilol regardless of NYHA class. Secondary: Not reported
Jabbour et al[100] β-blockers (bisoprolol, carvedilol, metoprolol)	OL, XO Patients with NYHA class I to III heart failure with a subgroup of patients with coexisting COPD	N=51 16 weeks	Primary: Post-bronchodilator FEV_1 Secondary: Not reported	Primary: FEV_1 was significantly higher in patients receiving bisoprolol vs carvedilol, both in those with coexisting COPD (P<0.01) and without (P=0.02). There was a significant difference between all patients receiving carvedilol versus those receiving metoprolol (P=0.04), however, when compared for coexisting COPD, there was no difference in FEV_1. There was no significant difference for all patients, those with COPD, or those with CHF only when metoprolol and bisoprolol were compared.
MERIT-HF Study Group[101] MERIT-HF Metoprolol CR/XL 12.5 mg up to 200 mg QD vs placebo	DB, MC, PC, RCT Symptomatic patients 40 to 80 years in NYHA class II to IV, with LVEF of 40% or less stabilized on standard therapy (diuretic and vasodilator)	N=3,991 1 year	Primary: All-cause mortality, all-cause mortality in combination with all-cause admission to hospital (time to first event) Secondary: Not reported	Primary: Study was stopped early on the recommendation of the independent safety committee. All-cause mortality was significantly lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%] vs 217 [11.0 %] deaths, RR, 0.66; 95% CI, 0.53 to 0.81; P=0.00009). There were significantly fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132; RR, 0.59; 95% CI, 0.45 to 0.78; P=0.0002) and deaths from worsening heart failure (30 vs 58; RR, 0.51; 95% CI, 0.33 to 0.79; P=0.0023). Study drug was permanently stopped early in 13.9% of the patients in the metoprolol CR/XL group and in 15.3% of patients in the placebo group (RR, 0.90; 95% CI, 0.77 to 1.06). Secondary: Not reported
Goldstein et al[102] MERIT-HF	Sub group analysis of	N=795	Primary: All-cause	Primary: There were 45 deaths (11.7% per patient year of follow-up) with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Metoprolol CR/XL 12.5 mg, titrated up to 200 mg QD vs placebo	MERIT-HF Patients with NYHA Class III to IV heart failure with LVEF <25%	1 year	mortality, composite of all-cause mortality and all-cause admission to hospital (time to first event) Secondary: Not reported	metoprolol and 72 deaths (19.1%) with placebo. Metoprolol decreased total mortality by 39%, sudden death by 45% and death due to worsening heart failure by 55%. Metoprolol also decreased the combined end points of all-cause mortality or all-cause hospitalization by 29%, all-cause mortality or hospitalization for worsening heart failure by 44% and cardiac death or nonfatal MI by 46%. Metoprolol reduced the total number of hospitalizations (all-cause) by 27% (0.709 vs 0.965 per patient year of follow up; P=0.0037). During the up titration phase of the trial, the cumulative numbers of patients hospitalized (all-cause) were: 17 vs 21 after two weeks, 28 vs 30 after four weeks, 39 vs 40 after six weeks, 46 vs 56 after eight weeks and 76 vs 102 after three months. The total number of hospitalizations for cardiovascular causes was reduced by 34% (0.475 vs 0.715 per patient year of follow up; P=0.0005) and for worsening heart failure by 45% (0.273 vs 0.497; P<0.0001). Improvement in NYHA functional class was recorded in 46.2 vs 36.7% of patients receiving metoprolol and placebo (P=0.0031). Secondary: Not reported
Waagstein et al[103] MDC Metoprolol 5 mg BID, titrated up to 100 to 150 mg/day vs placebo	DB, MC, PC, PG, RCT Patients 16 to 75 years of age with symptomatic dilated cardiomyopathy, an ejection fraction <40%	N=383 18 months	Primary: Combined all-cause mortality and clinical deterioration to a point at which cardiac transplantation would normally be offered as a	Primary: Thirty eight patients receiving placebo reached the primary endpoint compared to 25 patients receiving metoprolol, which corresponded to a risk reduction of 34% (95% CI, -6 to 62; P=0.058). With regard to the individual endpoints, 21 patients met the non-fatal endpoint of need for heart transplantation; two and 19 patients receiving metoprolol and placebo (P=0.0001). During the 12 or 18 months of follow up, all-cause mortality were 23 and 21 patients receiving metoprolol and placebo (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and being treated with diuretics, ACE inhibitors and nitrates		treatment option Secondary: Cardiac function, exercise capacity, QOL, hospital admission or emergency visits for HF treatment	Secondary: There was a significantly greater increase in ejection fraction with metoprolol compared to placebo by six and 12 months (P value not reported). QOL improved significantly more with metoprolol compared to placebo (P=0.01). With metoprolol, exercise capacity was significantly greater at six and 12 months compared to baseline (P=0.0006 and P=0.0007). With placebo there was a significant improvement from baseline at six months (P=0.007), but not at 12 months (P=0.46). The difference between the two treatments was significant only at 12 months (P=0.046). There was no difference between the treatments in the number of patients readmitted to the hospital (28 vs 20%; P=0.12), but the number of readmissions for all patients in the group was significantly lower with metoprolol (83 vs 51) as was the mean number of readmissions per patient (0.47 vs 0.28; P<0.04).
Di Lenarda et al[104] Metoprolol 142±44 mg QD vs carvedilol 12.5 mg to 50 mg BID	OL, PG, RCT Symptomatic (>12 months) patients with stable dilated cardiomyopathy, LVEF of ≤40% and who poorly responded to chronic treatment with metoprolol plus conventional	N=30 12 months	Primary: Improvement in left ventricular function and remodeling Secondary: Effects on symptoms, QOL, exercise tolerance, ventricular arrhythmias	Primary: LVEF significantly improved in the carvedilol group (7±3%) compared to the metoprolol group (-1±2%; P=0.045). LV end-systolic volume was significantly improved in the carvedilol group (-7±5) compared to the metoprolol group (6±4 mL/m^2; P=0.047). There was not a significant difference in LV end-diastolic volume observed between the carvedilol (-8±7) and the metoprolol group (7±6 mL/m^2; P=0.053). Secondary: There was not a significant difference observed in the NYHA class, the Heart Failure Score, the Minnesota “Living With Heart Failure” Questionnaire and submaximal exercise tolerance did not significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	therapy (metoprolol plus ACE inhibitor, digitalis, diuretics), persistent moderate-to-severe left ventricular dysfunction and reduced exercise tolerance			change between the carvedilol and metoprolol groups. Carvedilol, compared to metoprolol, demonstrated a positive effect on ventricular ectopic beats (-12±9 vs 62±50 n/h; P=0.05) and couplets (-0.5±0.4 vs 1.5±0.6 n/h; P=0.048), but not a significant effect on episodes of nonsustained ventricular tachycardia (-0.02±0.03 vs 0.03±0.01).
Maack et al[105] Metoprolol 12.5 to 100 mg BID vs carvedilol 3.125 to 25 mg BID	OL, XO Patients with stable NYHA class I to III heart failure due to ischemic or idiopathic dilated cardiomyopathy and an LVEF of <35%	N=80 6 months	Primary: Change in LVEF and change in baseline hemodynamic properties (left ventricular end diastolic, end systolic volume, NYHA class) Secondary: Not reported	Primary: After six months of treatment, LVEF improved in the carvedilol group (32±3 to 36±4%; P<0.05 vs baseline) and in the metoprolol group (27±4 to 30±5%; P<0.05 vs baseline). There was not a statistical difference between the agents. There were no differences between the groups in left ventricular end diastolic, end systolic volume, NYHA functional class or any other hemodynamic parameters at rest. Secondary: Not reported
Metra et al[106] Metoprolol 5 to 100 mg BID vs carvedilol 3.125 to 50 mg BID	DB, PRO, RCT Symptomatic (≥6 months) patients with CHF caused by ischemic or nonischemic cardiomyopathy, NYHA class II to IV, LVEF ≤35%	N=150 15 months	Primary: Change in LVEF Secondary: Hemodynamic variables at rest and peak exercise, maximal and submaximal	Primary: Both agents significantly increased LVEF from baseline (P<0.001 for both), but carvedilol increased LVEF significantly greater at the than metoprolol (10.9±11 vs 7.2±7.7%; P=0.038). Secondary: At the end of the study, both agents carvedilol and metoprolol increased stroke volume and stroke work indexes and decreased mean pulmonary artery pressure, pulmonary wedge pressure, and heart rate from baseline (all P<0.05 from baseline). However, the increase in

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All patients continued on their usual treatment for heart failure.	and a peak oxygen uptake ≤25 mL/kg-1/min-1 and on constant background therapy (furosemide and ACE inhibitor or ARB) for 1 week prior to the study		exercise tolerance, QOL, NYHA functional class, frequency of death and urgent transplantation	stroke volume and stroke work indexes during exercise and the decreases in mean pulmonary artery pressure and pulmonary wedge pressure at both rest and exercise were greater with carvedilol than with metoprolol (all P<0.05). Carvedilol increased rest and exercise cardiac index from baseline (both P<0.05). Heart rate declined with both drugs at rest and exercise, but the decrease in exercise heart rate with carvedilol was greater than with metoprolol (P<0.05 for the difference between the groups). Both metoprolol and carvedilol significantly improved NYHA class, 6-minute walk distance, and QOL scores from baseline (all P<0.05), and there were no differences between the two treatments. Overall, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent urgent transplantation.
Hypertension				
Reim et al[107] Acebutolol 400 mg QD vs propranolol 160 mg QD	DB, MC, XO Patients 18 to 70 years with essential HTN and blood pressure of >150/90 mm Hg	N=18 14 weeks	Primary: Blood pressure and heart rate during ergometer exercise test Secondary: Not reported	Primary: There was not a significant difference observed between the acebutolol and propranolol groups in decreases in blood pressure (systolic and diastolic) and heart rate at rest (P=0.123, P=0.230 and P=0.210, respectively). At the ergometer 25 watt load, heart rate and DBP were not significantly different between acebutolol and propranolol (P=0.087 and P=0.068, respectively), but SBP was significantly lower in the acebutolol group (P=0.042) At the higher ergometer loads of 50 and 75 watts, acebutolol had a significantly lower increase in SBP and heart rate compared to propranolol during exercise (50 watts: P=0.004 and P=0.012, respectively; 75 watts: P=0.005 and P=0.001, respectively), but there was not a significant difference observed between the groups in DBP in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the 50 and 75 watt loads (P=0.057 and P=0.058, respectively). At the highest ergometer load of 100 watts, acebutolol significantly reduced systolic and DBPs and heart rate compared to propranolol (P=0.003, P=0.001, and P=0.001, respectively). Secondary: Not reported
Fogari et al[108] Weeks 1 to 4: Atenolol 50 mg QD vs chlorthalidone 12.5 mg QD Weeks 5 to study end: atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose combination product)	RCT, SB Patients 61 to 80 years inadequately controlled (SBP >170 mm Hg and/or DBP >100 mm Hg) on antihypertensive medications	N=38 6 months	Primary: Changes in blood pressure Secondary: Not reported	Primary: After the first four weeks, atenolol (from 177.5 to 161.1 mm Hg) significantly reduced blood pressure compared to baseline, but chlorthalidone did not (from 176.6 to 179.1 mm Hg). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to previous therapies (P<0.001 for all comparisons). The combination atenolol-chlorthalidone therapy significantly reduced mean standing SBP and DBP, supine SBP and DBP, supine and standing heart rate, compared to atenolol and chlorthalidone monotherapy (P<0.001 or P<0.01 for all comparisons). Mean blood pressure reduction obtained by the atenolol and chlorthalidone combination product was 30/15 mm Hg in the standing position (P<0.001). Serum potassium increased with atenolol-chlorthalidone (4.45 mEq/L) compared to chlorthalidone alone (4.01 mEq/L; P<0.001). Secondary: Not reported
Leonetti et al[109] Atenolol 50 mg QD	DB, RCT Patients 24 to 68	N=28 16 weeks	Primary: Changes in blood pressure	Primary: Mean supine blood pressure was significantly reduced in all treatment groups compared to placebo: 153±18/93±9 mm Hg for atenolol 50 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atenolol 100 mg QD vs chlorthalidone 12.5 mg QD vs atenolol and chlorthalidone 50-12.5 mg QD (fixed-dose combination product)	years with mild to moderate HTN (WHO stage I or II), with supine DBP ≥95 mm Hg at the end of the 4-week washout period		Secondary: Not reported	patients, 155±22/91±8 mm Hg for atenolol 100 mg patients, 148±17/93±11 mm Hg for chlorthalidone 12.5 mg patients, and 144±16/89±6 mm Hg for the atenolol-chlorthalidone combination patients. All of the changes in blood pressure were significant (P<0.01) versus placebo. Supine SBP was lower with atenolol-chlorthalidone than with the atenolol 100 mg alone (P<0.05). Upright SBP was lower with atenolol-chlorthalidone than with atenolol 50 mg alone (P<0.05) and atenolol 100 mg alone (P<0.05). Mean supine heart rate was 77±7 bpm after placebo which decreased to 69±10 bpm (P<0.01) after atenolol 50 mg, to 67±6 bpm (P<0.01) after atenolol 100 mg, to 77±10 bpm (P=not significant, was not reported) after chlorthalidone alone. Chlorthalidone alone demonstrated a significant reduction in serum potassium levels compared to placebo (3.88 vs 4.09 mEq/L; P<0.05) and no change when the atenolol-chlorthalidone combination was compared to placebo (3.98 vs 4.09; P=not significant, value was not reported). Chlorthalidone alone and atenolol-chlorthalidone demonstrated a significant increase in serum uric acid levels compared to placebo (4.90±1.52 mg/dL, 5.07±1.33 mg/dL, respectively, vs 4.24±1.12 for placebo; P<0.05 for both). All treatments were well tolerated. Some adverse events reported included dyspnea, precordial discomfort and cold extremities. Incidence, severity and P values were not reported.
Nissinen et al[110] Atenolol 100 mg QD plus chlorthalidone 25 mg in the	DB, RCT Patients with newly diagnosed	N=23 16 weeks	Primary: Changes in blood pressure and heart rate	Primary: Each of the active drug combinations lowered standing, supine, and post-exercise blood pressure significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morning vs atenolol and chlorthalidone 100-25 mg in the morning (fixed-dose combination product) vs placebo	mild to moderate HTN (supine DBP 100 mm Hg on ≥3 occasions)		Secondary: Not reported	statistical difference between the active treatment regimens (P value not significant). Each of the active drug combinations lowered standing, supine, and post-exercise heart rate significantly compared to placebo at two and four weeks (P<0.001, P<0.01 and P<0.05). There was not a statistical difference between the active treatment regimens (P value not significant). Side effects did not differ between treatment groups and placebo in terms of frequency or severity. Reported side effects included dizziness, headache and tiredness. Secondary: Not reported
Johnson et al[111] Atenolol 50 to 100 mg QD for 9 weeks, followed by atenolol 50 to 100 mg QD and HCTZ 12.5 to 25 mg QD for 9 weeks vs HCTZ 12.5 to 25 mg QD for 9 weeks, followed by HCTZ 12.5 to 25 mg QD and atenolol 50 to 100 mg QD for 9 weeks	RCT Patients 17 to 65 years of age mild to moderate essential HTN	N=368 15 to 18 weeks	Primary: Blood pressure lowering effect of drug initiation order: the addition of a β-blocker to a thiazide versus the addition of a thiazide to a β-blocker Secondary: Not reported	Primary: When analyzed by order of initiation of the two drugs, the response to HCTZ and atenolol was greater overall than that seen for atenolol and HCTZ (P=0.0007 and P<0.0001). This study suggests that initiation of HCTZ followed by atenolol results in greater blood pressure lowering as compared with initiation in the reverse order, with differences that are potentially clinically important. Secondary: Not reported
Dhakam et al[112] Atenolol 50 mg QD vs	DB, RCT, XO Never-treated subjects with isolated systolic	N=16 17 weeks	Primary: Change in central blood pressure	Primary: There was not a statistically significant difference observed in the change in aortic SBP between the nebivolol and atenolol groups (125±3 vs 127±3 mm Hg; P=0.4), but both agents were significantly better than placebo (131±2 mm Hg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebivolol 5 mg QD vs placebo QD	HTN		Secondary: Change in peripheral blood pressure, AIx, aPWV and N-terminal proBNP.	There was not a statistically significant difference observed in the change in aortic DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.3), but both agents were better than placebo (82±2 mm Hg). Secondary: There was not a statistically significant difference observed in the change in brachial SBP between the nebivolol and atenolol groups (136±3 vs 137±3 mm Hg; P=0.4), but both agents were significantly better than placebo (149±3 mm Hg). There was not a statistically significant difference observed in the change in brachial DBP between the nebivolol and atenolol groups (75±2 vs 73±2 mm Hg; P=0.5), but both agents were better than placebo (82±2 mm Hg). There was a statistically significant reduction in AIx in the atenolol group compared to the nebivolol group (32±2 vs 28±2%; P=0.4), but both agents were significantly better than placebo (22±2%). There was not a statistically significant difference observed in the reduction of aPWV in the atenolol group compared to the nebivolol group (8.9±0.3 vs 9.1±0.3 m/s; P=0.2), but both agents were significantly better than placebo (10.0±0.4 m/s; P was not reported). There was not a statistically significant difference observed in the rise in N-terminal pro-BNP in the atenolol group compared to the nebivolol group (157 vs 138 pg/mL; P=0.6), but both agents were significantly better than placebo (75 mg/mL).
Fogari et al[113] Atenolol 50 mg QD vs	DB, PG, RCT Patients 18 to 70 years of age with stable type 2	N=30 6 months	Primary: Changes in blood pressure, heart rate, 24-hour urinary C-	Primary: Both atenolol and nebivolol significantly reduced blood pressure and heart rate from baseline (P<0.001 for all measures), but there was not a significant difference between the treatment groups at weeks 0, 2, and 24 (P>0.05 for all measures).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebivolol 5 mg QD	diabetes (HbA_{1c} ≤8% during previous 6 months with diet and/or oral therapy stable for ≥6 months), and mild to moderate HTN (DBP ≥95 and <116 mm Hg) at the end of the 4-week run-in period with placebo		peptide excretion, HbA_{1c}, plasma glucose, lipid levels Secondary: Euglycemic hyperinsulinemic clamp test (body glucose utilization)	There no significant changes from baseline in mean 24-hour urinary C-peptide excretion, HbA_{1c}, plasma glucose, and lipid levels (P>0.05). There were also no significant differences observed between treatment groups in any of these measures (P>0.05). Secondary: There was not a significant decrease from baseline in mean values for whole body glucose utilization observed in neither the atenolol group nor the nebivolol group (mean decrease of 0.9 vs 2.6%, respectively; P>0.05) and the groups were significant from each other (P>0.05).
Dietz et al[114] Atenolol 50 to 100 mg QD vs aliskiren 150 to 300 mg QD vs aliskiren 150 to 300 mg and atenolol 50 to 100 mg QD	DB, MC, RCT Patients ≥18 years of age with HTN (mean sitting DBP ≥95 and <110 mm Hg)	N=694 12 weeks	Primary: Changes in mean sitting SBP and mean sitting DBP, rates of blood pressure control (<140/90 mm Hg), pulse pressure and pulse rate, plasma renin concentration, plasma renin activity Secondary: Not reported	Primary: Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting SBP by 17.3 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P=0.039) or atenolol monotherapy (difference, -3.0 mm Hg; P=0.034). There was no difference between mean sitting SBP reductions with aliskiren and atenolol monotherapy (difference, -0.1 mm Hg; P=0.954). Treatment with aliskiren and atenolol combination therapy led to a significantly greater reduction in mean sitting DBP by 14.1 mm Hg compared to aliskiren monotherapy (difference, -2.9 mm Hg; P<0.001), but not atenolol monotherapy (difference, -0.5 mm Hg; P=0.545). Reductions in mean sitting DBP with atenolol were larger compared to those observed with aliskiren (difference, 2.4 mm Hg; P=0.003). Rates of blood pressure control were higher with aliskiren and atenolol combination therapy (51.3%) compared to aliskiren monotherapy (36.1%, P<0.001) or atenolol monotherapy (42.2%, P=0.009). There was no significant difference in blood pressure control rates between aliskiren and atenolol monotherapy (P=0.388).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean pulse pressure was reduced by 3.0 mm Hg with aliskiren and atenolol combination therapy and aliskiren monotherapy. Atenolol monotherapy did not affect pulse pressure. Aliskiren monotherapy did not affect pulse rate. Significant mean reductions in pulse rate of >10 bpm were observed with atenolol monotherapy and the aliskiren and atenolol combination (P<0.001 vs aliskiren monotherapy for both). Aliskiren monotherapy increased plasma renin concentration by 241% and aliskiren/atenolol increased plasma renin concentration by 85% (P=0.010 vs aliskiren). Atenolol monotherapy decreased plasma renin concentration by 24% (P<0.001 vs aliskiren and aliskiren/atenolol). Aliskiren, atenolol and aliskiren/atenolol reduced plasma renin activity by 65, 52, and 61%, respectively. Secondary: Not reported
Wald et al[115] Atenolol 25 mg QD vs lisinopril 5mg QD vs lisinopril 5 mg and atenolol 25 mg QD vs placebo	DB, DD, RCT, XO Patients ≥ 40 years enrolled in a HTN or anticoagulation clinic	N=47 16 weeks	Primary: Reduction in blood pressure Secondary: Not reported	Primary: The mean reductions in SBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 16.1, 12.5 and 22.9 mm Hg, respectively. The mean reductions in DBP in the atenolol alone, lisinopril alone and atenolol plus lisinopril groups were 9.8, 6.8 and 13.9 mm Hg, respectively. The reductions with lisinopril plus atenolol group were significantly higher than either agent as monotherapy (P<0.001). Secondary: Not reported
Pareek et al[116]	AC, MC, OL, RCT	N=190	Primary: Change in SBP	Primary: At the end of four weeks, the mean change in SBP (-30.0±10.4 vs -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atenolol 25 to 50 mg QD vs amlodipine 2.5 to 5 mg and atenolol 25 to 50 mg QD	Adults with either untreated or pretreated essential HTN	12 weeks	and DBP Secondary: Not reported	25.08±9.05; P=0.008) and DBP (-18.10±7.45 vs -14.78±7.48; P=0.021) was significantly greater in the low-dose combination therapy as compared to the low-dose monotherapy. At the end of 12 weeks, the mean SBP (127.82±8.90 vs 138.0±14.4; P=0.001) and mean DBP (81.73±8.78 vs 87.35±5.50; P=0.011) were significantly lower in the high-dose combination group as compared to the high-dose monotherapy group. Secondary: Not reported
Chapman et al[117] ASCOT-BPLA Atenolol 50 to 100 mg titrated to target blood pressure <140/90 mm Hg (or <130/90 mm Hg in diabetic patients); bendro-flumethiazide* plus potassium 1.25 to 2.5 mg plus doxazosin were added for additional blood pressure control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen vs amlodipine 5 to 10 mg titrated to target blood pressure <140/90 mm Hg	Subanalysis of ASCOT-BPLA evaluating effects of spironolactone on treatment-resistant HTN Patients 40 to 79 years of age with HTN and ≥3 cardiovascular risk factors, with SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (not on antihypertensive therapy) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (on antihypertensive therapy)	N=1,411 1.3 years	Primary: Change in DBP and SBP, adverse effects Secondary: Not reported	Primary: Spironolactone-treated patients lead to a significant 21.9 mm Hg reduction in SBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 20.8 to 23.0 mm Hg; P<0.001). Spironolactone-treated patients lead to a significant 9.5 mm Hg reduction in DBP among patients whose blood pressure was previously uncontrolled on at least three other antihypertensive drugs (95% CI, 9.0 to 10.1; P<0.001). Spironolactone-treated patients exhibited small but significant decreases in sodium, LDL-C and TC as well as increases in potassium, glucose, creatinine and HDL-C (P<0.05). The most common adverse effect reported in the trial was gynecomastia in men (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(or <130/90 mm Hg in diabetic patients); perindopril 4 to 8 mg and doxazosin were added for additional control; if blood pressure remained elevated on the 3 above drugs, spironolactone 25 mg was added to the regimen				
Pepine et al[118] INVEST Atenolol (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add trandolapril (step 4) (non-calcium antagonist strategy) vs verapamil SR (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy)	Post hoc analysis of INVEST Patients with essential HTN	N=22,576 24 months	Primary: Risk for adverse outcome associated with baseline factors, follow-up blood pressure and drug treatments Secondary: Not reported	Primary: Previous heart failure (adjusted HR, 1.96), as well as diabetes (HR, 1.77), increased age (HR, 1.63), United States residency (HR, 1.61), renal impairment (HR, 1.50), stroke/TIA (HR, 1.43), smoking (HR, 1.41), MI (HR, 1.34), PVD (HR, 1.27), and revascularization (HR, 1.15) predicted increased risk. Follow-up SBP <140 mm Hg (HR, 0.82) or DBP <90 mm Hg (HR, 0.70) and trandolapril with verapamil SR (HR, 0.78 and 0.79) were associated with reduced risk. Secondary: Not reported
Hilleman et al[119] Monotherapy (atenolol, HCTZ,	MA (82 trials) Patients with mild-to-moderate essential HTN	N=not reported ≥4 weeks	Primary: Absolute change in supine DBP from baseline	Primary: The mean absolute decrease in supine DBP ranged from 9.7 to 13.3 mm Hg with verapamil showing the greatest effect and captopril the least. When studies were weighted by sample size, amlodipine and benazepril, atenolol, lisinopril, and verapamil showed the greatest blood

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captopril, enalapril, lisinopril, amlodipine, diltiazem, nifedipine, verapamil) vs amlodipine and benazepril (fixed-dose combination)			Secondary: Percent of patients who achieved blood pressure control, safety	pressure effect. Secondary: The average percentage of patients defined as controlled after treatment varied from 53.5 to 79.0%, with amlodipine and benazepril (74.3%) and lisinopril (79.0%) showing the highest percentage control (P=0.096). The incidence of adverse events ranged from 12.1 to 41.8%, with lisinopril and verapamil showing the lowest incidences (12.1% and 14.1%, respectively) and nifedipine the highest incidence. Lisinopril demonstrated significantly less overall side effects compared to nifedipine (P=0.030). Nifedipine demonstrated a higher withdrawal rate due to side effects compared to atenolol, HCTZ, enalapril, amlodipine, and diltiazem (P=0.002). Although amlodipine and benazepril had the lowest rate of withdrawals due to adverse events, lack of significant change was due to the low number of cohorts available for analysis.
Davidov et al[120] Betaxolol 10 to 40 mg QD vs propranolol 40 to 160 mg BID	DB, MC, RCT Patients 21 to 73 years with mild to moderate HTN (supine DBP of 95 to 115 mm Hg)	N=141 24 weeks	Primary: Change in blood pressure and heart rate Secondary: Not reported	Primary: Both betaxolol and propranolol significantly reduced SBP from baseline (7±2.5 and 7±2.0 mm Hg; P<0.01 for both). Both betaxolol and propranolol significantly reduced DBP from baseline (11±0.9 and 9±1.2 mm Hg; P<0.01 for both). Both betaxolol and propranolol significantly heart rate from baseline (6±1.3 and 7±1.1 bpm; P<0.01 for both). At the end of the study, there was not a significant difference in response between groups. Secondary: Not reported
Czuriga et al[121]	MC, PG, RCT,	N=273	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
NEBIS Bisoprolol 5 mg QD vs nebivolol 5 mg QD	SB Patients 30 to 65 years with mild to moderate HTN, a DBP 95 to 110 mm Hg and a SBP ≤180 mm Hg at the end of the placebo run-in period who were either newly diagnosed or previously treated hypertensives and required a change of therapy in consequence of side-effects or poor compliance	16 weeks	Percentage of responders achieving DBP normalization (≤90 mm Hg) or a DBP reduction of at least 10 mm Hg and heart sitting rate Secondary: Adverse events, symptom questionnaire	There was not a significant difference between percentage of responders between the nebivolol group (92%) and the bisoprolol group (89.6%). There was not a significant difference in the mean change in blood pressure observed between the nebivolol and bisoprolol (SBP: -20.5±12.9 vs -20.0±12.0 mm Hg, respectively; P=0.7434) and DBP (-15.7±6.4 vs -16.0 ± 6.8 mm Hg, respectively; P=0.8230). There was not a significant difference in mean heart rate observed between the nebivolol (68.7±8.5 per minute) and the bisoprolol group (68.1±7.5 per minute). Secondary: There was not significant difference in rates of adverse events reported between the nebivolol (eight patients [5.8%]) and the bisoprolol group (12 patients [8.9%]; P>0.05). All adverse events were either mild (55%) or moderate (45%) in intensity. Both treatments demonstrated a significant reduction in the basal score index at visit 5 (nebivolol, -0.7 vs bisoprolol, -0.5; P<0.02), but there was no significant difference between treatment groups (P>0.05).
Stoschitzky et al[122] Bisoprolol 10 mg on day 1, then 5 mg QD vs carvedilol 50 mg on day 1, then 25 mg BID vs	DB, PC, RCT, XO Male patients between 22 and 34 years with a height between 177 and 189 cm, and body weight between 66 and 86 k	N=16 1 week	Primary: Heart rate and blood pressure at rest and exercise Secondary: Effects on nocturnal melatonin release, QOL	Primary: Compared to baseline, heart rate at exercise was decreased at three hours after the first dose by bisoprolol (-24%), carvedilol (-17%) and nebivolol (-15%); (P<0.05 for each group). Bisoprolol was significantly better than nebivolol (P<0.05). Compared to baseline, heart rate at exercise was decreased at 24 hours after the first dose by bisoprolol (-18%), carvedilol (12 hours; -15%) and nebivolol (-13%); (P<0.05 for each group). There was not a statistical significance observed between the groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebivolol 10 mg on day 1, then 5 mg QD				Compared to baseline, heart rate at exercise was decreased at 24 hours after the respective last dose at the end of one week of chronic administration by bisoprolol (-14%), carvedilol (12 hours; -15%) and nebivolol (-13%); (P<0.05 in all cases). There was not a statistical significance observed between the groups. All of the agents significantly decreased SBP both at rest and exercise at three and 24 hrs after the first dose as well at 24 hr after the last dose after seven days of chronic administration (P<0.05 in all cases). None of the agents had a significant effect on DBP at rest or at exercise. Secondary: Compared to placebo, nocturnal melatonin release was decreased by bisoprolol (-44%, P<0.05) whereas nebivolol (-16%) and carvedilol (-19%) had no effect. Total QOL with carvedilol (8.0±0.8) was slightly but significantly lower than that with placebo (8.6±0.4), nebivolol (8.5±0.6) and bisoprolol (8.4±0.5); (P<0.05 in all cases).
Lewin et al[123] Bisoprolol and HCTZ 5-6.25 mg QD (fixed-dose combination product) vs placebo	MC, PC Adult patients with stable mild to moderate (sitting DBP 95 to 114 mm Hg) essential HTN	N=36 4 weeks	Primary: Changes in 24-hr ambulatory daytime and nighttime blood pressure Secondary: Not reported	Primary: There were statistically significant reductions in blood pressure and pulse (P<0.01) at weeks two and four of treatment. There were statistically significant reductions (P<0.01) in 24 hr SBP and DBP, daytime and nighttime blood pressure, compared to the end of the placebo phase. There was a reduction in systolic and diastolic load also (P<0.01). The combination was well tolerated. The scores from the overall QOL questionnaire indicated an improvement with the combination (P=0.02).
Benetos et al[124] Bisoprolol and HCTZ 2.5-6.25 mg QD (fixed-dose	DB, MC, PG, RCT Patients over 60	N=164 12 weeks	Primary: Changes in blood pressure, heart rate,	Primary: Both bisoprolol and HCTZ and amlodipine significantly reduced SBP (-20.0±13.7 and -19.6±14.2 mm Hg, respectively; P<0.001) and DBP (-4.5±7.4 and -2.4±8.4 mm Hg, respectively from baseline to week 12,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product) vs amlodipine 5 mg QD	years with supine SBP 160 to 210 mm Hg and DBP <90 mm Hg		adverse events, QOL scores Secondary: Not reported	but there was not a significant difference between the agents (SBP; P=0.85 and DBP; P=0.09). Bisoprolol and HCTZ significantly reduced heart rate from baseline, but amlodipine did not (-7.6±8.4 [P<0.001] and -0.2±11.4 bpm, respectively). Bisoprolol and HCTZ significantly reduced heart rate when compared to amlodipine (P=0.0001). Overall adverse events were not significantly different between the amlodipine and the bisoprolol and HCTZ group (39 and 40%, respectively). Adverse events reported included headache, leg edema, fatigue and bradycardia but severity of events was not reported. Overall QOL scores were not significantly different between the amlodipine and the bisoprolol and HCTZ group. Secondary: Not reported
Prisant et al[125] Bisoprolol and HCTZ 2.5-6.25, 5-6.25, or 10-6.25 mg/day (fixed-dose combination product) vs enalapril 5, 10, or 20 mg vs amlodipine 2.5, 5, or 10 mg	DB, MC, PG, RCT Patients ≥21 years with mild to moderate essential HTN, (average sitting DBP 95 to 114 mm Hg) each treatment was once daily and titrated to effect	N=218 17 weeks	Primary: Mean change from baseline in SBP and DBP, lab measurements, adverse events, QOL questionnaire Secondary: Not reported	Primary: Mean decreases in SBP and DBP from baseline were 13.4/10.7 mm Hg for bisoprolol and HCTZ patients, 12.8/10.2 mm Hg for amlodipine patients, and 7.3/6.6 mm Hg for enalapril patients. The hypotensive effects were significant for all three groups (P<0.001). SBP and DBP mean changes from baseline for the bisoprolol and HCTZ group and the amlodipine group were greater than the change from baseline for the enalapril group (P<0.01). Response rates (DBP ≤90 mm Hg or ≥10 mm Hg decrease from baseline) were 71% for the bisoprolol and HCTZ group, 69% for the amlodipine group, and 45% for the enalapril group. The response rates for the bisoprolol and HCTZ and the amlodipine groups differed significantly from the enalapril group (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Twenty nine percent of bisoprolol patients had adverse experiences compared to 42% of amlodipine patients (P=0.12). Nearly 47% of enalapril patients had adverse experience compared to bisoprolol (P=0.04). Adverse events reported included headache, fatigue, peripheral edema, and dizziness. Drug related adverse events were 16% for the bisoprolol and HCTZ patients, 21% for the amlodipine patients, and 23% for the enalapril patients. There was no significant difference between the groups. Enalapril demonstrated a mean decrease from baseline of 7.9 mg/dL for TC (P=0.02 vs amlodipine) and 6.6 mg/dL for LDL-C (P=0.04 vs amlodipine) which were not significantly different from the increase from the bisoprolol and HCTZ group of 1.7 mg/dL (P=0.07 vs enalapril) for TC and +0.6 mg/dL in LDL-C. However, the increase in TGs was highest for bisoprolol and HCTZ-treated patients compared to amlodipine- and enalapril-treated patients (P=0.08, for bisoprolol and HCTZ vs enalapril). There was not a significant difference from baseline or between treatment groups in QOL scores: 0.9 for the bisoprolol and HCTZ group, 0.5 for the amlodipine group, and 2.3 for the enalapril group.
Frishman et al[126] Bisoprolol 2, 5, 10, or 40 mg QD vs HCTZ 6.25 or 25 mg QD vs bisoprolol plus HCTZ, all	DB, MC, PC, RCT Patients 21 years and older with mild to moderate essential HTN whose weight was 35% of the ideal for height and frame and	N=512 12 weeks	Primary: Changes in DBP and SBP Secondary: Not reported	Primary: All treatment groups (all doses) of bisoprolol, HCTZ and the combination of bisoprolol and HCTZ significantly reduced sitting DBP from baseline (P<0.01). The reduction in blood pressure was significantly greater as the doses of the bisoprolol, HCTZ and the combination of bisoprolol-HCTZ were increased (P<0.05). The combination bisoprolol and HCTZ significantly reduced sitting DBP compared to the separate agents as monotherapy (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
possible combinations	mean sitting DBP was stable and between 95 to 115 mm Hg			With higher doses of HCTZ, there was a significantly higher incidence of hypokalemia, defined as potassium <3.5 mmol/L (P<0.01). Incidence of hyperuricemia also significantly increased with the increase in HCTZ dose (P<0.01). Adverse events associated with hypokalemia and hyperuricemia were not reported. As the dose of bisoprolol was increased, the frequency and severity of adverse events reported significantly increased (P<0.05). Adverse events reported included asthenia, diarrhea, dyspepsia and somnolence, but severity of effects was not reported. Secondary: Not reported
Frishman et al[127] Bisoprolol 5 mg QD vs HCTZ 25 mg QD vs bisoprolol and HCTZ 5-6.25 mg QD (fixed-dose combination product) vs placebo	DB, MC, PC, PG, RCT Patients ≥21 years with mild to moderate (stage II or II) systemic HTN whose body weight was not >10% below or 35% above the ideal weight for height and frame, and were off all antihypertensive medications before study entry and sitting DBP was 95 to 115 mm Hg on 3	N=547 10 weeks	Primary: Changes in blood pressure and adverse events Secondary: Not reported	Primary: All active treatment groups significantly reduced sitting DBP and SBP from baseline compared to placebo (P<0.01). Addition of HCTZ 6.25 mg contributed significantly to the blood pressure lowering effects of bisoprolol 5 mg. The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting DBP from baseline (-12.6±0.5 mm Hg) compared to bisoprolol 5 mg alone (-10.5±0.5 mm Hg; P=0.02) and HCTZ 25 mg alone (-8.5±0.5 mm Hg; P<0.01). Bisoprolol 5 mg monotherapy was significantly better a reducing DBP compared to HCTZ 25 mg alone (P=0.03). The combination bisoprolol and HCTZ 5-6.25 mg produced a significantly greater reduction in mean sitting SBP from baseline (-15.8 mm Hg) compared to bisoprolol 5 mg alone (-10 mm Hg; P<0.01) and HCTZ 25 mg alone (-15.8 mm Hg; P<0.01). There was not a significant difference in mean reduction between bisoprolol 5 mg alone and HCTZ 25 mg alone. Bisoprolol and HCTZ 5-6.25 mg in combination had a 73% response

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	consecutive weekly visits			rate compared to 61% for the bisoprolol group and 47% for the HCTZ group. Bisoprolol and HCTZ 5-6.25 mg in combination was found to be significantly more effective compared to bisoprolol 5 mg or HCTZ 25 mg in all subgroups of patients regardless of age, race, gender, or smoking history (P>0.05 for all comparisons). Bisoprolol and HCTZ 5-6.25 mg in combination did not have an increase in frequency or severity of adverse events. The adverse events were comparable to that in the placebo group and frequency among groups was not significant. The most common adverse events reported were headache, dizziness, fatigue, and cough. Significantly greater number patients in the HCTZ 25 mg group (6.5%) experienced hypokalemia (potassium <3.4 mEq/L) compared to the bisoprolol 5 mg group (0.7%; P<0.01), the bisoprolol and HCTZ combination group (0.7%; P<0.01), and placebo (0%; P<0.01). Hyperglycemia occurred in 7.4% of patients in the HCTZ 25 mg group, which was significantly higher than in the placebo group (5.2%; P=0.03). Also, the incidence of hyperuricemia (uric acid >7.5 mg/dL) was significantly higher in the HCTZ 25 mg group (24.4%) compared to placebo (2.7%; P<0.01). Secondary: Not reported
Hamaad et al[128] Carvedilol 3.125 to 25 mg BID vs bisoprolol 1.25 to 10 mg	RCT Patients with stable LVEF of <40% and treated with diuretic and ACE inhibitor or ARB	N=31 12 weeks	Primary: Blood pressure, heart rate responses and both time and frequency domain heart rate variability	Primary: Carvedilol significantly reduced DBP from baseline to week 12 of therapy (stage 6), but bisoprolol did not: 10±16 mm Hg (P=0.045) and 7±16 mm Hg, respectively (P=0.159), but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly reduced SBP from baseline to week 12 of therapy (stage 6): 18±28 mm Hg (P=0.045) and 12±16

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD			Secondary: Not reported	mm Hg, respectively (P<0.003) but there was not a significant difference between groups. Both carvedilol and bisoprolol significantly decreased mean heart rate from baseline to week 12 of therapy (stage 6): 25±20 bpm and 23±10 bpm, respectively (P<0.01 for both agents vs baseline) but there was not a significant difference between groups (P=0.708). Neither carvedilol nor bisoprolol significantly increased four of the five heart rate variability indices measured including SDNN, RMSSD, low frequency power or high frequency power. But both carvedilol and bisoprolol significantly increased triangular index from baseline to week 12 of therapy (stage 6): 7±6 (P<0.01) and 5±6 (P=0.01), respectively, but there was not a significant difference between groups. Secondary: Not reported
Erdogan et al[129] Carvedilol 25 mg QD for 1 month vs nebivolol 5 mg QD for 1 month All patients went through a 10 day placebo run in period.	DB, PC, PRO, RCT, XO Patients with mild to moderate HTN	N=20 2 months	Primary: Blood pressure, heart rate Secondary: Safety	Primary: Treatment with carvedilol (133.8±9/86.6±8.6 mmHg) and nebivolol (134±8.7/85.6±7.4 mmHg) significantly decreased SBP and DBP compared to placebo (143.9±8.9/94.4±9.2 mmHg; P<0.05). There was no difference between carvedilol and nebivolol (P>0.05). Mean heart rate was significantly decreased after initiating treatment with carvedilol (70.2±5.2 bpm) and nebivolol (64.9±3.9 bpm) compared to placebo (78.8±5.2; P<0.05). Secondary: No adverse events were reported with either treatment.
Saunders et al[130] Labetalol 100 to 800 mg BID	DB, PG Patients with mild to moderate HTN	N=153 Duration not specified	Primary: Blood pressure, heart rate Secondary:	Primary: Labetalol was significantly better than propranolol at the end of monotherapy at lowering DBP (P<0.05) but there was no difference in lowering SBP.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs propranolol 40 to 320 mg			Not reported	Propranolol was significantly better at lowering heart rate compared to labetalol (P<0.01). No difference in the decrease in blood pressure after a diuretic was added. Secondary: Not reported
McAreavey et al[131] Labetalol 200 mg QD up to 1,600 mg BID vs prazosin 0.5 mg QD up to 10 mg BID vs hydralazine 12.5 mg QD up to 100 mg BID vs methyldopa 125 mg QD up to 1,000 mg BID vs placebo Minoxidil as add on therapy was given to men only.	DB, PG, RCT Patients with inadequately controlled HTN while receiving atenolol 100 mg/day and bendrofluazide* 5 mg/day	N=238 6 months	Primary: Comparative safety and efficacy, target blood pressure <140/95 mm Hg Secondary: Not reported	Primary: Target blood pressure was reached in 25% of patients receiving hydralazine, 23% of patients receiving minoxidil, 19% of patients receiving prazosin, 17% of patients receiving methyldopa and zero percent of patients receiving placebo (P values not reported). Labetalol had the highest withdrawal rate compared to the other treatments with 78% (P<0.05). Minoxidil had the second highest withdrawal rate with 57% (P<0.05), due to fluid retention. There were no significant differences in withdrawal rates among the other treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Doses were titrated upward at 2 week intervals until target blood pressure or maximum dose was reached.				
Wright et al[132] AASK Metoprolol 50 to 200 mg/day vs ramipril 2.5 to 10 mg/day vs amlodipine 5 to 10 mg/day	DB, MC, RCT Patients were self-identified African Americans aged 18 to 70 years with HTN and a GFR between 20 and 65 mL/min/ 1.73 m^2 and no other identified cause of renal insufficiency	N=1,094 3-6.4 years	Primary: Rate of change in GFR (grouped by usual blood pressure [MAP goal 102 to 107 mm Hg] vs lower blood pressure [≤92 mm Hg]) Secondary: Clinical composite outcome (reduction in GFR by 50% or more, ESRD, or death)	Primary: No significant difference in primary outcome was reported between the usual blood pressure group compared to the lower blood pressure group (P=0.24). None of the drug group comparisons showed consistently significant differences in the GFR slope. Secondary: The lower blood pressure goal did not significantly reduce the rate of the clinical composite outcome (risk reduction for lower blood pressure group, 2%; 95% CI, -22 to 21; P=0.85). Ramipril resulted in significant risk reductions in the clinical composite outcomes compared to amlodipine (38%; 95% CI, 14 to 56; P=0.004) and metoprolol (22%; 95% CI, 1 to 38; P=0.04). There was no significant difference in the clinical composite outcome between the amlodipine and metoprolol groups.
Dafgard et al[133] Metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product) vs HCTZ 50 mg QD in the	DB, MC, RCT Patients with essential HTN (WHO stages I or II) not adequately controlled (≥160/95 mm Hg) on HCTZ 25	N=31 32 weeks	Primary: Blood pressure, heart rate, adverse events, laboratory values Secondary: Not reported	Primary: After the eight week run-in period with HCTZ 25 mg alone, the mean supine blood pressure was significantly reduced from 183/110 to 172/103 mm Hg (P<0.01/P<0.01). The increased dose of HCTZ 50 mg following the run-in period did not further significantly reduce the mean blood pressure (165/104 mm Hg). A small but statistically significant reduction in supine heart rate was seen when the HCTZ dose was increased from 25 to 50 mg (82 down to 78 bpm; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morning vs HCTZ 25 mg QD in the morning	mg/day			After the 12 week double-blind period, the mean supine blood pressure was 153/98 mm Hg in the HCTZ 50 mg group. After the 12 week follow-up period, there was not any additional decrease in blood pressure (153/97 mm Hg). Fixed-dose combination product of metoprolol and HCTZ produced a significant reduction in supine blood pressure after 12 weeks of therapy from 172/105 mm Hg on HCTZ 25 mg alone to 154/97 mm Hg on the combination therapy (P<0.001/P<0.01). Similar results were found with the standing blood pressure reductions, from 165/108 to 147/97 mm Hg (P<0.001/P<0.001). After the eight week run-in period, the supine heart rate was 80 bpm which decreased to 64 bpm with the metoprolol and HCTZ fixed-dose combination (P<0.001). The values for standing heart rate demonstrated similar significant reductions (85 to 66 bpm; P<0.001). After the additional 12 week follow-up, the patients in the metoprolol and HCTZ fixed-dose combination group did not demonstrate a significant further reduction in heart rate or blood pressure in any position. Both agents were tolerated and the most common adverse events reported included insomnia, headache, tiredness, and shortness of breath. The majority of events were mild, few were moderate, and none were severe. The only significant changes in laboratory values occurred with the HCTZ 25 and 50 mg groups, where an increase in serum uric acid was observed from 0.30 to 0.34 and 0.35 mmol/L, respectively (P<0.01 and P<0.05; respectively). Secondary: Not reported
Smilde et al[134]	DB, PG, RCT, XO	N=37	Primary: Changes in	Primary: Both group 1 and 2 significantly reduced DBP (P<0.01) from baseline

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Metoprolol 400 mg QD in the morning for 5 weeks, followed by metoprolol and HCTZ 200-25 mg QD in the morning (fixed-dose combination product) (group 1) vs metoprolol and HCTZ 200-25 mg QAM for 5 weeks (fixed-dose combination product), followed by metoprolol 400 mg QD in the morning for 5 weeks (group 2)	Patients <65 years with essential HTN (supine DBP ≥95 mm Hg) not controlled on metoprolol 200 mg alone	15 weeks	DBP, SBP, and heart rate Secondary: Not reported	and the two groups were not significantly different from each other. The combination products significantly reduced SBP from baseline (P<0.05, P<0.01 depending on comparison) Group 2 significantly reduced heart rate at the end of the study compared to baseline (P<0.05). Clinically relevant changes in laboratory parameters or mean body weight were not observed between the groups. Secondary: Not reported
Liedholm et al[135] Metoprolol and HCTZ 100-12.5 mg BID (fixed-dose combination product) (group A) vs metoprolol and HCTZ 100-25 mg BID (fixed-dose combination product) (group B) <u>Extended Study:</u> Metoprolol and HCTZ 100-12.5 mg, 2 tablets QD in	RCT Patients 18 to 72 years with mild to moderate essential HTN (WHO I or II) <u>Extended Study:</u> OL Those patients who participated in the initial trial, had poor blood pressure control on existing antihypertensive	N=55 12 weeks <u>Extended Study:</u> N=49 6 months	Primary: Change in blood pressure Secondary: Not reported	Primary: In group A, there was a significant decrease in supine blood pressure from 189/112 to 172/105 mm Hg with metoprolol monotherapy and further reduction to 148/92 mm Hg with the metoprolol and HCTZ 100-12.5 mg (P<0.001/P<0.001). In group B, there was a significant decrease in supine blood pressure from 184/111 to 170/104 mm Hg with metoprolol monotherapy and further reduced to 152/96 mm Hg with metoprolol and HCTZ 100-25 mg (P<0.01/P<0.05) after 12 weeks. Supine heart rate fell in group A from 78 to 68 bpm with metoprolol monotherapy (P<0.001). No further heart rate reduction was noted with the metoprolol and HCTZ 100-12.5 mg. In group B, supine heart rate fell from 76 to 69 bpm (P<0.05). No further heart rate reduction was seen with metoprolol and HCTZ 100-25 mg. In group A, serum sodium fell from 143 to 140 mmol/L (P<0.01). In

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
the morning (fixed-dose combination product)	therapy, and were being treated with a β-blocker and additional diuretic therapy			group B, serum potassium fell with from 4.4 to 4.0 mmol/L (P<0.001). Extended Study: After six months of extended the therapy, there was no further significant reductions in supine or standing blood pressure, but there was a reduction in standing DBP from 97 to 95 mm Hg (P<0.05).
Materson et al[136] Metoprolol 50, 100 or 200 mg BID vs hydralazine 25, 50 or 100 mg BID vs methyldopa 250, 500 or 1,000 mg BID vs reserpine 0.05, 0.10 or 0.25 mg QD All patients received HCTZ 25 to 100 mg QD.	DB, MC, RCT Men ≥60 years with HTN not currently receiving antihypertensive therapy and DBP 90 to 114 mm Hg and SBP <240 mm Hg or a DBP <100 mm Hg and a SBP <240 mm Hg if currently taking antihypertensive therapy and the blood pressure criteria was met after ≥2 weeks without medication	N=690 12 months	Primary: The average reduction in SBP and DBP, the number of patients achieving the goal blood pressure, the average change in heart rate Secondary: The rates of drug intolerances, adverse effects	Primary: Across all four treatments, there was an additional average reduction in BP of 13.1/10.6 mm Hg. The average reduction in SBP from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.5±10.1 (P<0.001), -15.0±13.7 (P<0.001), -13.0±15.4 (P<0.001) and -12.7±11.5 (P<0.001), respectively. There was no significant difference in SBP reductions among the different treatments (P=0.43). The average reduction in DBP from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were -11.3±5.9 (P<0.001), -10.6±6.3 (P<0.001), -10.6±6.7 (P<0.001) and -9.8±6.3 (P<0.001), respectively. There was no significant difference in DBP reductions among the different treatments (P=0.59). The average change in heart rate from baseline to endpoint for hydralazine, methyldopa, metoprolol and reserpine were 1.4±10.5 (P value not significant), -1.6±9.3 (P value not significant), 15.9±11.9 (P<0.05) and -7.9±10.7 (P<0.05), respectively. There was a significant difference in change in heart rate among the different treatments (P<0.001). The percentage of patients achieving the goal blood pressure at endpoint with hydralazine, methyldopa, metoprolol and reserpine were 85.3, 81.7, 76.9 and 72.3%, respectively (P=0.28). Secondary: Drug intolerance, defined as adverse effects prompting dose reduction or discontinuation, was present in 23.3% of patients not achieving goal blood pressure compared to 2.8% of those who did (P<0.001). This was significant with hydralazine, methyldopa and metoprolol, but not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with reserpine. There were 27 (10%) treatment discontinuations due to adverse effects (hydralazine [n=3], methyldopa [n=8], metoprolol [n=9] and reserpine [n=7]). There were two treatment discontinuations with methyldopa and one with reserpine due to depression. The overall incidence of volunteered moderate or severe adverse effects, not prompting treatment discontinuation, was significantly greater (P<0.01) with methyldopa (31%) and hydralazine (25%) compared to reserpine (15%) or metoprolol (9%).
Greathouse[137] Nebivolol 5, 10 or 20 mg QD vs placebo All patients entered a 4 to 6 week washout, SB, placebo run in period.	DB, PC, PG, RCT Patients ≥18 years of age with stage I to II HTN (average sitting DBP ≥95 and ≤109 mm Hg)	N=811 12 weeks	Primary: Change in mean sitting DBP at trough drug concentration (24±2 hours after the previous morning's dose) Secondary: Mean changes in trough sitting SBP, responder rate (mean trough SBP <90 mm Hg or a decrease of ≥10 mm Hg from baseline), safety and tolerability	Primary: Least squares mean reductions in trough sitting DBP at week 12 were significantly greater with all doses of nebivolol compared to placebo (P=0.002 for 5 mg and P<0.001 for 10 and 20 mg). All doses of nebivolol reduced peak sitting DBP in a dose-dependent manner. The least squares mean reductions in peak sitting DBP following treatment with 5, 10, and 20 mg of nebivolol were -10.5, -11.6, and -12.2 mm Hg (P<0.001 vs placebo for all). Secondary: All doses of nebivolol resulted in least squares mean reductions in trough sitting SBP from baseline, with only the 20 mg dose reaching significance compared to patients receiving placebo (P<0.001). All doses of nebivolol reduced peak sitting SBP in a dose-dependent manner. The least squares mean reductions with nebivolol in peak sitting SBP were -7.7, -10.7 and -4.7 mm Hg (P=0.004 vs placebo for 10 mg and P<0.001 vs placebo for 20 mg). Significantly more patients receiving nebivolol were treatment responders compared to placebo (66.0 [P=0.009 vs placebo], 66.8 [P=0.005 vs placebo] and 68.9% [P=0.002 vs placebo] vs 49.3%). A total of 27 (36.0%) and 311 (42.5%) patients receiving placebo and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nebivolol experienced an adverse event. The most commonly reported adverse events for the combined nebivolol group (all doses) compared to the placebo group were headache (7.5 vs 5.3%), fatigue (3.8 vs 1.3%) and nasopharyngitis (3.7 vs 4.0%).
Neutel et al[138] Nebivolol 5, 10 or 20 mg/day vs placebo	DB, PC, PG, RCT Patients ≥18 years of age with stage I to II HTN who were inadequately controlled by antihypertensive medication (SBP ≥90 and ≤109 mm Hg) and stable on a regimen of antihypertensive medications consisting of ≥1 and ≤2 of an ACE inhibitor, ARB or diuretic	N=669 12 weeks	Primary: Change in mean clinic sitting DBP at trough (24±3 hours after previous morning's dose) Secondary: Change in mean trough sitting SBP and mean sitting DBP, change in mean sitting SBP at peak (two to three hours after dosing), mean peak and trough supine and standing DBP and SBP, mean 24 hour DBP and SBP as measured by ambulatory blood pressure monitoring, responder rate (sitting SBP <90 mm Hg or an	Primary: Addition of nebivolol to background antihypertensive therapy led to significant additional blood pressure reductions compared to placebo. Nebivolol 5, 10, and 20 mg significantly lowered trough sitting DBP by -3.3, -3.5, and -4.6 mm Hg, respectively (P<0.001 for all doses). Secondary: Nebivolol 5, 10 and 20 mg significantly lowered trough sitting SBP by -5.7, -3.7, and -6.2 mm Hg, respectively (P<0.001 for 5 and 20 mg and P=0.015 for 10 mg). Reductions in trough blood pressure in the standing and supine positions were comparable to sitting blood pressure reductions for all nebivolol doses. All doses of nebivolol also significantly reduced peak sitting DBP (-3.2, -4.0, and -4.3 mm Hg) and sitting SBP (-5.7, -5.6, and -5.9 mm Hg) at week 12 compared to placebo (P<0.001 for both). Reductions from baseline to week 12 in peak blood pressure with nebivolol in both supine and standing positions were consistent with those for sitting DBP and sitting SBP (data not reported). After 12 weeks, the proportion of patients responding to treatment was significantly higher with nebivolol 5 mg (53.0%; P=0.028), 10 mg (60.1%; P=0.001) and 20 mg (65.1%; P<0.001) compared to placebo (41.3%). In addition, a significantly higher percentage of patients receiving nebivolol achieved blood pressure control (<140/90 mm Hg) (43.0, 41.3 and 52.7 vs 29.3%; P≤0.029).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			absolute reduction ≥10 mm Hg)	
Weiss et al[139] Nebivolol 1.25 to 30 or 40 mg/day vs placebo	Pooled analysis of 3 PC, RCT, SB Patients with stage I-II HTN	N=2,016 ≥12 weeks	Primary: Mean change from baseline in sitting DBP, sitting SBP, and heart rate at 12 weeks Secondary: Safety	Primary: Compared to placebo, reductions in DBP, SBP, and heart rate were significantly greater with nebivolol at the recommended dosages of 5-30/40 mg/day (P<0.001 for all). Secondary: The most commonly reported adverse events were headache (7.1 vs 5.9%), fatigue (3.6 vs 1.5%), and nasopharyngitis (3.1 vs 4.4%).
Rosei et al[140] Nebivolol 5 mg QD vs lisinopril 20 mg QD	DB, MC, PG, RCT Patients between 24 and 65 years with mild to moderate uncomplicated essential HTN that was newly diagnosed, or previous antihypertensive therapy was withdrawn at >1 month before active treatment, and had a sitting DBP of >95 and <114 mm Hg	N=65 12 weeks	Primary: Response rates, changes in sitting blood pressure Secondary: Standing blood pressure, sitting and standing heart rate	Primary: There was not a significant difference in response rates observed between the two treatment groups. Both treatment groups significantly reduced sitting SBP (P<0.0001) and DBP (P<0.0001) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, DBP was significantly lower in the nebivolol group compared to the lisinopril group (P<0.05). Secondary: There was not a significant difference observed between treatment groups in standing blood pressure measurements. Both treatment groups significantly reduced sitting heart rate (P<0.01) throughout the study compared to baseline but there were no significant differences observed between the treatment groups at most visits, but at week eight, heart rate were significantly lower in the nebivolol group compared to the lisinopril group (P<0.05).
Mazza et al[141]	DB, MC, PG, RCT	N=168	Primary: Change in sitting	Primary: There was not a significant difference observed between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nebivolol 2.5 to 5 mg QD vs amlodipine 5 to 10 mg QD	Patients between 65 to 89 years of age with mild to moderate essential HTN and DBP ranging from 95 to 114 mm Hg	16 weeks	blood pressure, response rates Secondary: Standing blood pressure changes, standing and sitting heart rate changes	amlodipine and nebivolol treatments groups in changes in sitting DBP (blood pressure values and P values not reported). At weeks four and eight, a slightly lower sitting SBP was observed in per-protocol patients in the amlodipine groups vs those in the nebivolol group (blood pressure values not reported, P<0.005). Response rates were not significantly difference between the amlodipine group and the nebivolol group (86 vs 88%, respectively). The percentage of patients who reached normalization (blood pressure <140/90 mm Hg) was no significant between the amlodipine and the nebivolol groups (47 vs 50%). Secondary: There were significant differences in standing blood pressure observed between the groups. Heart rate was significantly lower in the nebivolol group compared to the amlodipine group at all treatment visits (P<0.001). Patients in the amlodipine group experienced a significantly greater rate of headache (seven vs five patients) and ankle edema (12 vs zer0 patients) compared to the patients in the nebivolol group (P<0.05 for both).
Van Bortel et al[142] Nebivolol 5 mg QD vs losartan 50 mg QD If after 6 weeks, DBP was not normalized, then HCTZ 12.5 mg QD was added to therapy	DB, MC, PG, RCT Patients <70 years of age with DBP at randomization between 95 and 114 mm Hg	N=314 12 weeks	Primary: Effects on blood pressure, overall QOL Secondary: Comparison of different aspects of QOL	Primary: At the end of 12 weeks, both nebivolol and losartan significantly reduced SBP compared to baseline (P<0.0001 for both), but the agents were not significantly different from each other. Both agents also significantly decreased DBP compared to baseline (P<0.0001), but nebivolol significantly reduced DBP compared to losartan (P<0.02). At the end of 12 weeks, both nebivolol and losartan significantly improved QOL scores compared to baseline (P<0.007), but the agents were not significantly different from each other.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: At week 12 there was not a significant difference observed in the individual questions of the QOL questionnaire between the groups. Questions inquired about headaches, lightheadedness, sleepiness, flushing, and sexual function.
Van Bortel et al[143] Nebivolol vs ACE inhibitor, ARB, β-blocker, calcium channel blocker, or placebo	MA 12 RCTs involving >25 patients with essential HTN where nebivolol 5 mg QD was compared to placebo or other active drugs for >1 month	N=2,653 Duration varied	Primary: Antihypertensive effect and tolerability Secondary: Not reported	Primary: Overall, higher response rates were observed with nebivolol than all other antihypertensive agents combined (OR, 1.41; 95% CI, 1.15 to 1.73; P=0.001) and compared to the ACE inhibitors (OR, 1.92; 1.30 to 2.85; P=0.001), but response rates to nebivolol were similar to β-blockers (OR, 1.29; 95% CI, 0.81 to 2.04; P=0.283), calcium channel blockers (OR, 1.19; 95% CI, 0.83 to 1.70; P=0.350) and losartan (OR, 1.35; 95% CI, 0.84 to 2.15; P=0.212). Overall, a higher percentage of patients obtained normalized blood pressure with nebivolol compared to the other antihypertensive agents combined (OR, 1.35; 95% CI, 1.07 to 1.72; P=0.012). A higher percentage of patient receiving nebivolol obtained normalized blood pressure compared to losartan (OR, 1.98; 95% CI, 1.24 to 3.15; P=0.004) and calcium channel blockers (OR, 1.96; 95% CI, 1.05 to 1.96; P=0.024), but not when compared to other β-blockers (OR, 1.29; 95% CI, 0.81 to 1.65; P=0.473). Overall, the percentage of adverse events was significantly lower with nebivolol compared to the other antihypertensive agents combined (OR, 0.59; 95% CI, 0.48 to 0.72; P<0.001) and similar to placebo (OR, 1.16; 95% CI, 0.76 to 1.67; P=0.482). In comparing nebivolol to the individual treatments, nebivolol had a lower percentage of adverse events compared to losartan (OR, 0.52; 95% CI, 0.30 to 0.89; P=0.016), the other β-blockers (OR, 0.56; 95% CI, 0.36 to 0.85; P=0.007) and calcium channel blockers (OR, 0.49; 95% CI 0.33 to 0.72; P<0.001), but was similar to ACE inhibitors (OR, 0.75; 95% CI 0.52 to 1.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Veterans Administration Cooperative Study Group on Antihypertensive Agents[144] Nadolol 80 to 240 mg QD in the morning vs bendro-flumethiazide 5 to 10 mg* QD in the morning vs nadolol and bendro-flumethiazide*	DB, RCT Men 20 to 69 years with pretreatment DBP of 95 to 114 mm Hg	N=365 12 weeks	Primary: Changes in blood pressure, change in blood pressure among races, heart rate, adverse events, laboratory values Secondary: Not reported	Primary: DBP of <90 mm Hg was achieved in 49% of the nadolol patients, 46% of the bendroflumethiazide patients, and 85% of the combination patients. There was a significantly higher percentage of patients who achieved the DBP goal compared to the nadolol alone group and bendroflumethiazide group alone (P<0.01 for both). The reduction in SBP was significantly greater in the combination group compared to the nadolol alone and bendroflumethiazide group (-25.3±1.4, -10.5±1.6, and -17.4±1.7 mm Hg, respectively; P<0.001 for both) and bendroflumethiazide produced a significantly greater reduction compared to nadolol alone (P<0.01). The reduction of DBP in white patients was significantly greater than the decrease in African American (decrease of 15.6 vs 9.6 mm Hg, respectively; P<0.001). In addition, 77% of white patients achieved DBP of <90 mm Hg compared to only 31% of African American patients (P<0.001). Adverse events were infrequent. The most common were impotence, lethargy, weakness, and postural dizziness, which occurred more often with bendroflumethiazide than nadolol. Significant reductions in average heart rate from baseline were observed with nadolol alone (decrease by 16.1 bpm; P<0.001) and with the combination product (decrease by15.8 bpm; P<0.001). Serum potassium levels significantly decreased from baseline in the bendroflumethiazide group by -0.57±0.06 mEq/L (P<0.001) and in the combination group by -0.44±0.05 mEq/L (P<0.001). Serum uric acid levels significantly increased from baseline in the bendroflumethiazide group by 1.7±0.2 mg/dL (P<0.001), in the nadolol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group by 0.4±0.1 mg/dL (P<0.01) and in the combination group by -1.9±0.1 mg/dL (P<0.001). Fasting glucose levels significantly increased from baseline in the bendroflumethiazide group by 6.1±2.1 mg/dL (P<0.001) and in the combination group by 7.4±1.1 mg/dL (P<0.001). Cholesterol significantly increased from baseline in the bendroflumethiazide group by 11.5±4.3 mg/dL (P<0.001). TGs significantly increased from baseline in the bendroflumethiazide group by 34.6±14.8 mg/dL (P<0.01), in the nadolol group by 38.7±13.2 mg/dL (P<0.01) and in the combination group by 67.8±11.9 mg/dL (P<0.001). Secondary: Not reported
Frick et al[145] Penbutolol 40 mg BID vs propranolol 160 mg BID	DB, XO Patients 29 to 64 years of age with HTN	N=20 13 weeks	Primary: Blood pressure, heart rate Secondary: Not reported	Primary: Penbutolol significantly reduced supine and standing blood pressures (both SBP and DBP) from baseline (P<0.05). Propranolol also significantly reduced blood pressures from baseline (SBP: P<0.02 and diastolic: P<0.01), but there was not significant difference between agents. Penbutolol significantly reduced supine and standing heart rates from baseline (from 76±10 to 61±9; P<0.001 and from 85±13 to 67±8; P<0.001, respectively. Propranolol also significantly reduced heart rates from baseline (to 59±8; P<0.001 and to 63±7; P<0.001, respectively), but there was not significant difference between agents. Secondary: Not reported
Finnerty et al[146] Propranolol 80 mg to 320	SB Patients with	N=59 9 weeks	Primary: Percentage of patients	Primary: At study endpoint, the DBP below 90 mm Hg was achieved in all 20 patients (100%) treated with hydroflumethiazide plus reserpine, 13 of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD vs reserpine 0.125 mg to 0.25 mg QD vs methyldopa 500 mg to 2,000 mg QD All patients received hydro-flumethiazide* 50 or 100 mg QD.	HTN unresponsive to hydroflumethiazide alone		achieving a DBP below 90 mm Hg Secondary: Not reported	the 19 patients (68.4%) treated with hydroflumethiazide plus methyldopa, and in 16 of the 20 patients (80%) treated with hydroflumethiazide plus propranolol. Secondary: Not reported
VA Cooperative Study[147] Propranolol 40 to 160 mg TID (P), propranolol 40- to 160 mg TID plus HCTZ 35 mg (P+T), propranolol 40 to 160 mg TID plus hydralazine 35 mg (P+H), or propranolol 40 to 160 mg TID plus HCTZ 35 mg plus hydralazine 35 mg (P+T+H) vs reserpine 35 mg plus HCTZ 35 mg (R+T)	DB, RCT Men 18 to 59 years with DBP of 90 to 114 mm Hg	N=450 18 months	Primary: Percent of patients who achieved a DBP <90 mm Hg at 6 months, heart rate, withdrawal rate Secondary: Not reported	Primary: At six months, significantly more patients in the R+T arm (88%) attained a DBP <90 mm Hg and ≥5 mm Hg less than the initial blood pressure compared to the P arm (52%; P<0.01) and the P+H arm (72%; P<0.05). The other arms: P+T (81%) and P+T+H (92%) were not significantly different than the R+T arm. The 12 and 18 month results do not have the statistical validity of the six months results due to the reduced sample size. The following percentage of patients attained DBP <90 mm Hg and ≥5 mm Hg less than the initial pressure: R+T=89.1 and 82.6%, P=59.5 and 58.1%, P+T=86.0 and 86.4%, P+H=67.4 and 76.1%, and P+T+H=89.4 and 91.8%. There was not a significance difference in heart rate reductions at six and 18 months between the groups (R+T=5.0±1.3 and 5.0±1.3 mean change in heart rate, P=9.1±1.3 and 9.2±1.8, P+T=8.8±1.2 and 6.3±1.5, P+H=8.9±1.3 and 7.8±1.5, and P+T+H=5.9±1.1 and 7.7±1.5). Withdrawals for any reason were similar between the treatment arms

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and were not statistically significant (R+T=14 patients, P=11, P+T=12, P+H=14, and P+T+H=16).
Stevens et al[148] Dose-finding phase: Propranolol 80, 160, 240, or 320 mg/day in 2 divided doses vs propranolol and HCTZ 80-50, 160-50, 240-50, 320-50 mg/day in 2 divided doses (fixed-dose combination product) Double-blind phase: Propranolol and HCTZ (fixed-dose combination product) vs propranolol vs HCTZ	DB, PG, RCT Patients with mild to moderate essential HTN (DBP 100 to 125 mm Hg)	N=158 25 weeks	Primary: Mean changes of SBP and DB, heart rate, lab values Secondary: Not reported	Primary: After the 12 week dose finding-phase, 94% of patients had a decrease ≥10 mm Hg in DBP. The mean SBP and DBP reduced from 158.0 (±17.3)/105.6 (±6.0) mm Hg to 131.5 (±14.4)/86.4 (± 6.7) mm Hg (P<0.001). After the 10 week portion of the study, there were significantly greater increases (P<0.05) in mean SBP or DBP with propranolol and HCTZ alone vs the combination product of propranolol and HCTZ from the end of the dose-finding to the last four biweekly visits to the mean of those visits, and to the last visit. The mean increases of SBP and DBP at the endpoint were: propranolol, 10.2/6.3 mm Hg; HCTZ 13.1/9.3 mm Hg; propranolol-HCTZ combination product 3/1.5 mm Hg. There was a significant decrease in heart rate as the dose of propranolol was increased thought the trial (P>0.30). The only lab value that showed a statistically significant change was serum chloride. The percent of patients that fell outside of the normal range were as follows: propranolol 6/36 (17%), HCTZ 14/37 (38%), and combination 4/28 (14%); P<0.05. Secondary: Not reported
de Leeuw et al[149] Verapamil SR and trandolapril 180-2 mg/day,	DB, MC, PC, RCT Patients 18 to 70	N=205 12 weeks	Primary: Changes in supine blood pressure,	Primary: Each of the three treatments was significantly more effective than placebo in reducing seated DBP. Changes in DBP were as follows: verapamil SR and trandolapril, -13 (95% CI, -16 to -9); atenolol and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
atenolol and chlorthalidone 100-25 mg/day, or lisinopril and HCTZ 20-12.5 mg/day (fixed-dose combination products) vs placebo All patients entered a SB, placebo 4 week run in period.	years of age with essential HTN (WHO I or II) newly or unsuccessfully treated, with supine DBP 101 to 114 mm Hg in week 4 of the run in period		standing blood pressure response rates, normalization rates Secondary: Not reported	chlorthalidone, -13 (95% CI, -16 to -9); lisinopril and HCTZ, -12 (95% CI, -15 to -9) and placebo, -3 (95% CI, -7 to 0) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Each of the three treatments was significantly more effective than placebo in reducing seated SBP. Changes in SBP were as follows: verapamil SR and trandolapril, -27 (95% CI, -33 to -21); atenolol and chlorthalidone, -28 (95% CI, -34 to -22); lisinopril and HCTZ, -23 (95% CI, -29 to -17) and placebo, -3 (95% CI, -9 to 3) (P=0.0001 for all vs placebo), but there was not a significance among the treatments (P values not reported). Effects on standing blood pressure demonstrated similar results as the effects on sitting blood pressure (P values not reported). Normalization of DBP (<90 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 33% [95% CI, 16 to 50; P<0.0005]; atenolol and chlorthalidone, 31% [95% CI, 14 to 48; P<0.002] and lisinopril and HCTZ, 25% [95% CI, 9 to 42; P<0.005]). Response rates (normalization of DBP or a reduction in DBP >10 mm Hg), corrected for placebo, were significantly higher with all treatments compared to placebo (verapamil SR and trandolapril, 40% [95% CI, 22 to 58; P<0.0001], atenolol and chlorthalidone, 44% [95% CI, 27 to 61; P<0.0001] and lisinopril and HCTZ, 37% [95% CI, 19 to 55; P<0.0002]). Secondary: Not reported
Casas et al[150] ACE inhibitor or ARBs compared to other antihypertensive drugs	MA (127 trials) Studies in adults that examined the effect of any	N=not reported 4.2 years (mean)	Primary: Doubling of serum creatinine, and ESRD	Primary: Treatment with ACE inhibitors or ARBs resulted in a nonsignificant reduction in the risk of doubling of creatinine vs other antihypertensives (P=0.07) with no differences in the degree of change of SBP or DBP between the groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(β-adrenergic blocking agents, α-adrenergic blocking agents, calcium-channel blocking agents, or combinations) vs ACE inhibitor or ARBs compared to placebo Specific agents and doses were not specified.	drug treatment with a blood pressure lowering action on progression of renal disease		Secondary: Serum creatinine, urine albumin excretion and GFR	A small reduction in ESRD was observed in patients receiving ACE inhibitors or ARBs compared to other antihypertensives (P=0.04) with no differences in the degree of change of SBP or DBP between the groups. Secondary: Small reductions in serum creatinine and in SBP were noted when ACE inhibitors or ARBs were compared to other antihypertensives (P=0.01). Small reduction in daily urinary albumin excretion in favor of ACE inhibitor or ARBs were reported when these agents were compared to other antihypertensives (P=0.001). Compared to other drugs, ACE inhibitors or ARBs had no effect on the GFR.
Baguet et al[151] Antihypertensive drugs (enalapril, ramipril, trandolapril, candesartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, HCTZ, indapamide SR*, atenolol, amlodipine, lercanidipine*, manidipine*, enalapril, ramipril, trandolapril, and aliskiren) Drugs were used as monotherapy, either at a	MA Patients greater than 18 years of age with mild or moderate essential HTN (SBP 140 to 179 mm Hg and/or DBP 90 to 109 mm Hg)	N=10,818 8 to 12 weeks	Primary: Weighted average reductions in SBP and DBP Secondary: Not reported	Primary: Data did not reflect outcomes from direct, head-to-head comparative trials or formal comparisons between drugs. Diuretics (-19.2 mm Hg; 95% CI, -20.3 to -18.0), calcium channel blockers (-16.4 mm Hg; 95% CI, -17.0 to -15.8) and ACE inhibitors (-15.6 mm Hg; 95% CI, -17.6 to -13.6) produced the greatest reductions in SBP from baseline (P values not reported). The magnitude of DBP reductions were generally similar among all drug classes; however, the greatest reductions in DBP from baseline were observed with the β-blocker, atenolol (-11.4 mm Hg; 95% CI, -12.0 to -10.9), calcium channel blockers (-11.4 mm Hg; 95% CI, -11.8 to -11.1) and diuretics (-11.1 mm Hg; 95% CI, -11.7 to -10.5) (P values were not reported). The weighted average reduction of SBP and DBP for each drug class

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fixed daily dosage or in increasing dosages. Although cicletanine*, furosemide and spironolactone were considered for inclusion, none of the trials relating to these agents satisfied all inclusion criteria.				were as follows: Diuretics: -19.2 (95% CI, -20.3 to -18.0) and -11.1 mm Hg (95% CI, -11.7 to -10.5), respectively. β-blockers: -14.8 (95% CI, -15.9 to -13.7) and -11.4 mm Hg (95% CI, -12.0 to -10.9), respectively. Calcium channel blockers: -16.4 (95% CI, -17.0 to -15.8) and -11.4 mm Hg (95% CI, -11.8 to -11.1), respectively. ACE inhibitors: -15.6 (95% CI, -17.6 to -13.6) and -10.8 mm Hg (95% CI, -11.9 to -9.7), respectively. ARBs: -13.2 (95% CI, -13.6 to -12.9) and -10.3 mm Hg (95% CI, -10.5 to -10.1), respectively. Renin inhibitor: -13.5 (95% CI, -14.2 to -12.9) and -11.3 mm Hg (95% CI, -11.7 to -10.9), respectively. Secondary: Not reported
Post Myocardial Infarction and Other Cardiovascular Outcomes Trials				
Gottlieb et al[152] Atenolol vs metoprolol vs propranolol vs other (not specified)	RETRO Patients discharged from the hospital with the diagnosis of an acute MI and on a β-blocker	N=69,338 2 years	Primary: Mortality rates at 1 and 2 year(s) Secondary: Not reported	Primary: β-blockers demonstrated a 40% overall reduction in mortality compared to those patient who did not receive β-blocker therapy. One year mortality rates in the three groups were metoprolol 8.32% (CI, 8.07 to 8.58, atenolol 8.16% (CI, 7.76 to 8.58), propranolol 9.55% (CI, 9.69 to 10.48), and other 9.19% (CI, 8.16 to 10.33). Two year mortality rates in the three groups were metoprolol 13.52% (CI, 13.21 to 13.84), atenolol 13.41% (CI, 12.91 to 13.93), propranolol 15.91% (CI, 14.83 to 17.05), and other 15.17% (CI, 13.88 to 16.56). There were no differences between atenolol and metoprolol at the end of the two years, both of which were statistically better than propranolol. Compared to metoprolol, patients discharged on propranolol had 15% increased mortality at one year and 18% increased mortality at two years, which were significantly higher than metoprolol.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Testa et al[153] (2014) Patients taking atenolol vs Patients not taking atenolol	Observational Patients aged ≥65 years with isolated HTN	N=972 12 years	Primary: Mortality Secondary: Not reported	Primary: Univariate analysis shows that elderly participants taking atenolol show greater mortality than those not taking atenolol (52.4 vs 66.7%; P=0.047). Cox regression analysis on 12-year mortality showed that age, number of diseases, number of drugs, basic activity of daily living ≥l%, and social support score were predictive; whereas female sex and Mini-Mental State Examination score were protective of long-term mortality. Additionally, pulse arterial pressure (HR, 1.02; 95% CI, 1.01 to 1.03; P=0.035) and atenolol use (HR, 1.89; 95% CI, 1.03 to 4.25; P<0.05) were predictive of long-term mortality. Secondary: Not reported
Black et al[154] CONVINCE Atenolol 50 mg QD vs verapamil ER 180 mg QD vs HCTZ 12.5 mg QD	AC, DB, MC, RCT Patients 55 years of age and older with HTN and ≥1 risk factor for cardiovascular disease	N=16,476 3 years	Primary: Composite first occurrence of acute MI, stroke or cardiovascular disease-related death Secondary: Cardiovascular endpoints expanded, all-cause mortality, cancer, hospitalization for bleeding, incidence of primary	Primary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment groups in the composite primary endpoint (HR, 1.02; 95% CI, 0.88 to 1.18; P=0.77). Secondary: There was no significant difference between the verapamil treatment group and the atenolol or HCTZ treatment group in rates of cardiovascular-related hospitalization (P=0.31), death (all-cause mortality) (P=0.32) and cancer rates (P=0.46). Patients treated with verapamil experienced a significantly higher rate of death or bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15 to 2.04; P=0.003). Primary endpoints did not differ significantly based on time of day (P=0.43).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			endpoints between 6AM and noon, adverse events	Patients treated with verapamil were more likely to withdraw for adverse events or symptoms than those treated with atenolol or HCTZ (P=0.02).
Dahlöf et al[155] LIFE Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200 to 95 to 115 mm Hg) and left ventricular hypertrophy	N=9,193 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality, hospitalization for angina or heart failure, revascularization procedures, resuscitated cardiac arrest, new-onset diabetes	Primary: SBP fell by 30.2 and 29.1 mm Hg in the losartan and atenolol groups, respectively (treatment difference, P=0.017) and DBP fell by 16.6 and 16.8 mm Hg, respectively (treatment difference, P=0.37). MAP was 102.2 and 102.4 mm Hg, respectively (P value not significant). Heart rate decreased more in patients assigned to atenolol than losartan (-7.7 vs -1.8 beats/minute, respectively; P<0.0001). Compared to atenolol, the primary composite occurred in 13.0% fewer patients receiving losartan (RR, 0.87; 95% CI, 0.77 to 0.98; P=0.021). While there was no difference in the incidence cardiovascular mortality (P=0.206) and MI (P=0.491), losartan treatment resulted in a 24.9% relative risk reduction in stroke compared to atenolol (P=0.001). Secondary: A 25% lower incidence of new-onset diabetes was reported with losartan compared to atenolol (P=0.001). There was no significant difference among the other secondary end points between the two treatment groups. Note: At end point or end of follow-up, 18 and 26% of patients on losartan were receiving HCTZ alone or with other drugs, respectively. In the atenolol group, 16 and 22% of patients were receiving HCTZ alone or with other drugs, respectively.
Julius et al[156] LIFE Black Subset Atenolol 50 to 100 mg QD vs	Post hoc analysis Patients 55 to 80 years old with essential HTN	N=523 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke	Primary: Compared to atenolol (11.2%), losartan in the United States African American population resulted in a greater incidence of the composite end point (17.4%; P=0.033). HRs favored atenolol across all parameters (P=0.246 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	(sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy		Secondary: Not reported	cardiovascular mortality, P=0.140 for MI, and P=0.030 for stroke). In African American patients, blood pressure reduction was similar in both groups, and regression of electrocardiographic-left ventricular hypertrophy was greater with losartan. Secondary: Not reported
Lindholm et al[157] LIFE Diabetic Subset Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD was added if needed for blood pressure control.	Post hoc analysis Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=1,195 ≥4 years	Primary: Composite of cardiovascular death, MI and stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a 24% decrease in the primary composite end point (P=0.031). Losartan treatment resulted in a 37% risk reduction in cardiovascular deaths vs atenolol (P=0.028). Losartan treatment resulted in a 39% risk reduction in all-cause mortality vs atenolol (P=0.002). Mean blood pressure fell to 146/79 mm Hg in losartan patients and 148/79 mm Hg in atenolol patients. Secondary: Mortality from all causes was 63 and 104 in the losartan and atenolol groups, respectively (RR, 0.61; P=0.002).
Kjeldsen et al[158] LIFE Isolated Systolic Hypertension Subset Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD HCTZ 12.5 to 25 mg QD	Post hoc analysis Patients 55 to 80 years old with isolated systolic HTN (SBP of 160 to 200 mm Hg and DBP <90 mm Hg) and left ventricular	N=1,326 ≥4 years	Primary: Composite of cardiovascular death, MI, or stroke Secondary: All-cause mortality	Primary: Compared to atenolol, losartan resulted in a trend towards a 25% reduction in the primary end point (P=0.06). Losartan treatment resulted in a 46% risk reduction in cardiovascular mortality (P=0.01) and 40% risk reduction in stroke compared to atenolol (P=0.02). There was no difference in the incidence of MI. Blood pressure was reduced by 28/9 and 28/9 mm Hg in the losartan and atenolol arms.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
was added if needed for blood pressure control.	hypertrophy			Secondary: Patients receiving losartan also had reductions in all-cause mortality (28%; P<0.046).
Fossum et al[159] ICARUS, a LIFE substudy Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=81 3 years	Primary: Amount and density of atherosclerotic lesions in the common carotid arteries and carotid bulb Secondary: Not reported	Primary: The amount of plaque decreased in the losartan group and increased in the atenolol group, though the difference between groups was not statistically significant (P=0.471). Patients in the atenolol group had a greater increase in plaque index compared to the losartan group, though the difference between groups was not statistically significant (P=0.742) Secondary: Not reported
Kizer et al[160] (LIFE substudy) Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=9,193 ≥4 years	Primary: Reduction in the risk of different stroke subtypes and neurological deficits Secondary: Not reported	Primary: The risk of fatal stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.032). The risk of atherothrombotic stroke was significantly decreased in the losartan group compared to the atenolol group (P=0.001). Comparable risk reductions were observed for hemorrhagic and embolic stroke but did not reach statistical significance. The risk of recurrent stroke was significantly reduced in the losartan arm compared to the atenolol arm (P=0.017). The number of neurological deficits per stroke was similar (P=0.68), but there were fewer strokes in the losartan group for nearly every level of stroke severity. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Wachtell et al[161] (LIFE substudy) Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need for blood pressure control.	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to 115 mm Hg) and left ventricular hypertrophy	N=8,851 (patients in LIFE with no baseline history of AF but at risk for AF) ≥4 years	Primary: Incidence of new-onset AF and outcome Secondary: Not reported	Primary: Significantly fewer patients in the losartan group experienced new-onset AF compared to the atenolol group (P<0.001). Randomization to losartan treatment was associated with a 33% lower rate of new onset AF independent of other risk factors (P<0.001). Patients in the losartan group had a 40% lower rate of composite events consisting of cardiovascular death, fatal or non-fatal stroke, and fatal or non-fatal MI (P=0.03). Significantly fewer strokes occurred in the losartan group compared to the atenolol group (P=0.01), and there was a trend toward fewer MIs in the losartan group (P=0.16). There was no significant difference in cardiovascular mortality between groups. In contrast, the atenolol group experienced significantly fewer hospitalizations for heart failure (P=0.004) and a trend toward fewer sudden cardiac deaths (P=0.07). Secondary: Not reported
Wachtell et al[162] (LIFE substudy) Atenolol 50 to 100 mg QD vs losartan 50 to 100 mg QD All patients received HCTZ 12.5 to 25 mg/day if need	DB, DD, PG, RCT Patients 55 to 80 years old with essential HTN (sitting SBP/DBP 160 to 200/95 to115 mm Hg) and left ventricular	N=342 (LIFE patients with AF at the start of the LIFE study) ≥4 years	Primary: Cardiovascular morbidity and mortality Secondary: Not reported	Primary: Patients with a history of AF had significantly higher rates of cardiovascular and all-cause mortality, fatal and non-fatal stroke, heart failure, revascularization and sudden cardiac death compared to patients without AF (P<0.001). Patients with a history of AF had similar rates of MI and hospitalization for angina pectoris (P≥0.209). The primary composite endpoint of cardiovascular mortality, stroke and MI occurred in significantly fewer patients in the losartan group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for blood pressure control.	hypertrophy			compared to the atenolol group (P=0.009). The difference in MI between groups was not significant. Treatment with losartan trended toward lower all-cause mortality (P=0.09) and fewer pacemaker implantations (P=0.065). Secondary: Not reported
Dahlöf et al[163] Hypertension (STOP) Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs placebo	DB, MC, RCT Swedish men and women 70 to 84 years old with treated or untreated essential HTN defined as SBP ≥180 mm Hg with a DBP of ≥90 mm Hg, or DBP >105 mm Hg irrespective of the SBP measured on 3 separate occasions during a 1-month placebo run-in phase in previously untreated patients	N=1,627 25 months	Primary: Frequency of stroke, MI, and other cardiovascular death Secondary: Not reported	Primary: The active treatments significantly reduced the number of all primary endpoints (94 vs 58; RR, 0.60; 95% CI, 0.43 to 0.85; P=0.0031), frequency of stroke (53 vs 29; RR, 0.53; 95% CI, 0.33 to 0.86; P=0.0081) and frequency of other cardiovascular deaths (13 vs 4; RR, 0.30; 95% CI, 0.07 to 0.97) compared to placebo. There was not a statistically significant decrease observed in the rate of MI between the active treatments and placebo (28 vs 25; RR, 0.87; 95% CI, 0.49 to 1.56). Secondary: Not reported
Hannson et al[164] HYPERTENSION-2	BE, MC, OL, RCT	N=6,614	Primary: Combined fatal	Primary: The combined fatal mortality endpoints occurred in 221of the 2,213

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(STOP) Conventional drug group Atenolol 50 mg QD, HCTZ 25 mg QD plus amiloride 2.5 mg QD, metoprolol 100 mg QD, or pindolol 5 mg QD vs Newer drug group ACE inhibitors (enalapril 10 mg QD or lisinopril 10 mg QD) or calcium channel blockers (felodipine 2.5 mg QD, or isradipine 2 to 5 mg QD)	Swedish men and women between 70 to 84 years old with treated or untreated essential with HTN on 3 separate occasions defined by SBP ≥180 mm Hg, DBP >105 mm Hg, or both	60 months	stroke, MI, and other fatal cardiovascular disease; combined fatal and nonfatal stroke, MI, and other cardiovascular Mortality Secondary: Not reported	patients in the conventional drugs group and in 438 of 4,401 in the newer drugs group (RR, 0.99; 95% CI, 0.84 to 1.16; P=0.89). The combined fatal and nonfatal mortality endpoints occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (RR, 0.96; 95% CI, 0.86 to 1.08; P=0.49). Secondary: Not reported
Dalhof et al[165] ASCOT-BPLA Atenolol 50 to 100 mg/day adding bendro-flumethiazide* 1.25 to 2.5 mg/day and potassium as needed vs amlodipine 5 to 10 mg/day adding perindopril 4 to 8 mg/day as needed If blood pressure was still not achieved, doxazosin 4	MC, OL, RCT Patients 40 to 79 years of age with HTN and ≥3 other cardiovascular risk factors (left ventricular hypertrophy, other specified abnormalities on ECG, type 2 diabetes, PAD, history of stroke or TIA, male, age ≥55 years,	N=19,257 5.5 years	Primary: Nonfatal MI (including silent MI) and fatal CHD Secondary: All-cause mortality, total stroke, primary end points minus silent MI, all coronary events, total cardiovascular events and procedures,	Primary: No statistically significant difference in nonfatal MI and fatal CHD was reported between the amlodipine plus perindopril group compared to the atenolol plus bendroflumethiazide groups (HR, 0.90; 95% CI, 0.79 to 12; P=0.1052). Secondary: Significantly greater reductions in the following secondary end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: all- cause mortality (P=0.0247), total stroke (P=0.0003), primary end points minus silent MI (P=0.0458), all coronary events (P=0.0070), total cardiovascular events and procedures (P<0.0001), and cardiovascular mortality (P=0.0010). There were no significant differences in nonfatal and fatal heart failure between the two treatment groups (P=0.1257).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to 8 mg/day was added to the regimen.	microalbuminuria or proteinuria, smoking, TC:HDL-C ratio ≥6, or family history of CHD)		cardiovascular mortality, nonfatal and fatal heart failure, effects on primary end point and on total cardiovascular events and procedures among prespecified subgroups Tertiary: Silent MI, unstable angina, chronic stable angina, PAD, life-threatening arrhythmias, development of diabetes, development of renal impairment	The study was terminated early due to higher mortality and worse outcomes on several secondary end points observed in the atenolol study group. Tertiary: Significantly greater reductions in the following end points were observed with amlodipine plus perindopril compared to atenolol plus bendroflumethiazide: unstable angina (P=0.0115), PAD (P=0.0001), development of diabetes (P<0.0001), and development of renal impairment (P=0.0187). There were no significant differences in the incidence of silent MI (P=0.3089), chronic stable angina (P=0.8323) or life-threatening arrhythmias (P=0.8009) between the two treatment groups. There was no significant difference in the percent of patients who stopped therapy because of an adverse event between the two treatment groups (overall 25%). There was, however, a significant difference in favor of amlodipine plus perindopril in the proportion of patients who stopped trial therapy because of a serious adverse events (2 vs 3%; P<0.0001).
Pepine et al[166] INVEST Atenolol 50 mg/day (step 1), then add HCTZ if needed (step 2), then increase doses of both (step 3), then add	MC, OL, RCT Patients with essential HTN	N=22,576 24 months	Primary: First occurrence of death (all cause), nonfatal MI or stroke Secondary: Cardiovascular	Primary: At 24 months, in the calcium antagonist strategy subgroup, 81.5% of patients were taking verapamil SR, 62.9% trandolapril, and 43.7% HCTZ. In the non-calcium antagonist strategy, 77.5% of patients were taking atenolol, 60.3% HCTZ, and 52.4% trandolapril. After a follow-up of 61,835 patient-years (mean, 2.7 years per patient), 2,269 patients had a primary outcome event with no statistically

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
trandolapril (step 4) (non-calcium antagonist strategy) vs verapamil SR 240 mg/day (step 1), then add trandolapril if needed (step 2), then increase doses of both (step 3), then add HCTZ (step 4) (calcium antagonist strategy) Trandolapril was recommended for all patients with heart failure, diabetes, or renal insufficiency.			death, angina, cardiovascular hospitalization, angina, blood pressure control (SBP/DBP <140/90 mm Hg or <130/85 mm Hg if diabetic or renal impairment), safety	significant difference between treatment strategies (9.93% in calcium antagonist strategy vs 10.17% in non-calcium antagonist strategy; RR, 0.98; 95% CI, 0.90 to 16; P=0.57). Secondary: There was no significant difference in the rate of cardiovascular death (P=0.94) or cardiovascular hospitalization (P=0.59) between the two treatment groups. At 24 months, angina episodes decreased in both groups, but the mean frequency was lower in the calcium antagonist strategy group (0.77 episodes/week) compared to the non-calcium antagonist strategy group (0.88 episodes/week; P=0.02). Two-year blood pressure control was similar between groups. The blood pressure goals were achieved by 65.0% (systolic) and 88.5% (diastolic) of calcium antagonist strategy patients and 64.0% (systolic) and 88.1% (diastolic) of non-calcium antagonist strategy patients. A total of 71.7% of calcium antagonist strategy patients and 70.7% of non-calcium antagonist strategy patients achieved an SBP <140 mm Hg and DBP <90 mm Hg. Both regimens were generally well tolerated. Patients in the calcium antagonist strategy group reported constipation and cough more frequently than patients in the non-calcium antagonist strategy group, while non-calcium antagonist strategy patients experienced more dyspnea, lightheadedness, symptomatic bradycardia and wheezing (all were statistically significant with P≤0.05).
Mancia et al[167] INVEST Atenolol 25 to 200 mg QD vs	MC, open blinded endpoint, PRO, RCT Patients with HTN, requiring drug therapy	N=22,576 24 months	Primary: Occurrence of death, nonfatal MI and nonfatal stroke Secondary:	Primary: Rates (death, nonfatal MI and nonfatal stroke) were similar for both treatment groups (P value not reported). Secondary: Rates of death, MI and stoke declined as the number of office visits for which blood pressure was controlled increased (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
verapamil SR 120 to 480 mg QD	(BP>140/90 or >130/80 mm Hg if diabetic or with renal impairment), and CAD		Blood pressure control rates	
Bangalore et al[168] INVEST Verapamil SR 120 to 480 mg QD vs atenolol 25 to 200 mg QD Trandolapril and/or HCTZ were added to control blood pressure.	INVEST substudy Patients 50 years of age and older with hypertension requiring drug therapy (blood pressure >140/90 or >130/80 mm Hg if diabetic or with renal impairment), and documented coronary artery disease	N=22,576 24 months	Primary: First occurrence of death, nonfatal MI, nonfatal stroke Secondary: Death, total MI, total stroke	Primary: No significant difference was observed between groups in the primary endpoint (P=0.30). Among patients with the primary outcome, no significant difference was observed between groups in the risk of death (P=0.94). There was no significant difference between groups in the risk of nonfatal MI (P=0.41). There was a trend toward a 29% reduction in the risk of nonfatal stroke in the verapamil group compared to the atenolol group (P=0.06). Secondary: The risks of fatal and nonfatal MI were similar between groups. No significant differences were observed between groups in fatal and nonfatal stroke (P=0.18).o
Iliuta et al[169] Betaxolol 20 mg/day vs metoprolol 100 mg BID	OL, MC Patients who were admitted for CABG surgery	N=1352 30 days	Primary: Mortality, in-hospital occurrence of AF, total hospital stay and immobilization (days) Secondary: Not reported	Primary: Betaxolol significantly decreased 30 day mortality (P=0.001) and in-hospital AF (P=0.0001) compared to metoprolol. Patients taking betaxolol were less likely to be hospitalized for >15 days (9.94 vs 13.27, P=0.01) or immobilized for >3 days (5.19 vs 8.26, p=0.002) compared to metoprolol. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jonsson et al[170] Carvedilol 6.25 to 25 mg BID vs atenolol 12.5 to 50 mg BID	OL, RCT Patients between 18 to 80 years of age with chest pain consistent with an acute MI, admitted to the hospital 24 hours after onset and a confirmed diagnosis with significant increase in cardiac enzymes	N=232 1.5±1.3 years	Primary: Change in global or regional LVEF after 12 months, cardiovascular endpoints, adverse events Secondary: Not reported	Primary: At baseline, mean global LVEF was 54.8% in the carvedilol and 53.0% in the atenolol group and increased after 12 months to 57.1% in the carvedilol and 56.0% in the atenolol group. There was not a significant difference between treatment groups for change in global or regional LVEF (values were not reported). There was not a significant difference in the rates of occurrence of the first serious cardiovascular events observed between the carvedilol and atenolol groups after adjustment for diuretic use (0.247 vs 0.299; RR, 0.83; 95% CI, 0.56 to 1.23; P=0.39). Of the nonserious adverse events reported, a greater incidence of colds hand and feet were reported in the atenolol group (38 [33.3%]) compared to the carvedilol group (24 [20%]; P=0.025). Secondary: Not reported
Pasternak et al[171] (2014) Carvedilol vs metoprolol succinate	RETRO Danish patients aged 50 to 84 years with HF and LVEF ≤40% who received carvedilol or metoprolol succinate treatment	N=11,664 Up to 3 years (Median 2.4)	Primary: All-cause mortality Secondary: Cardiovascular mortality	Primary: The cumulative incidence of all-cause mortality was 18.3 and 18.8% in the carvedilol and metoprolol groups, respectively. After adjustment for propensity score, the risk of mortality did not differ significantly between carvedilol and metoprolol users (aHR, 0.99; 95% CI, 0.88 to 1.11). Secondary: The risk of cardiovascular mortality was not significantly different between carvedilol and metoprolol users (aHR, 1.05; 95% CI, 0.88 to 1.26).
Olsson et al[172] Metoprolol 100 mg BID vs	MA (5 trials) Patients with a past history of MI	N=5,474 3 months to 3 years	Primary: All-cause mortality, sudden deaths Secondary:	Primary: Metoprolol significantly reduced all-cause mortality compared to placebo (188 vs 223 deaths; P=0.036). Metoprolol significantly reduced sudden deaths compared to placebo (62 vs 104 deaths; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			Not reported	Secondary: Not reported
Piccini et al[173] Amiodarone vs sotalol vs no antiarrhythmic drug (AAD)	RETRO Patients with CAD and AF	N=2,838 Median follow-up 4.2 years	Primary: All-cause mortality Secondary: Not reported	Primary: In unadjusted and adjusted settings, mortality rates were lower in patients treated with sotalol compared with amiodarone or no AAD. After adjustment for baseline characteristics only, the 1-year mortality rate was 10% in those treated with sotalol, 20% in those treated with amiodarone, and 14% in those treated with no AAD (no P-value reported). Landmark analysis at 60 days and one year was also performed. After adjustment and weighting, sotalol was associated with improved survival from 0 to 60 days compared with amiodarone (HR, 0.14; 95% CI, 0.06 to 0.32) but not at later time points (≥60 days or ≥1 year). Similarly, compared with no AAD therapy, sotalol was not associated with improved survival beyond 60 days. Cumulative survival after one year in patients treated with sotalol vs no AAD was also not improved (P=0.64). Secondary: Not reported
No authors listed (abstract)[174] Timolol vs placebo	DB, MC, PC, RCT Patients <75 years of age surviving an acute MI	N=1,884 12 to 33 months	Primary: All-cause mortality Secondary: Not reported	Primary: Long term treatment with timolol improved prognosis. A significant difference in life table mortality of 39.3% between treatments was observed (13.3 vs 21.9%; P=0.0003). The difference was due to a lower rate of sudden cardiac death with timolol compared to placebo (7.7 vs 13.9%; P=0.0001). Secondary: Not reported
Patel et al[175] β-blocker therapy (carvedilol, metoprolol	RETRO Medicare patients in the	N=2,198 (1099 propensity-matched	Primary: composite endpoint of all-cause mortality	Primary: Discharge prescriptions for β-blockers to older HF with preserved ejection fraction patients who were not receiving these drugs prior to admission had no association with the primary composite endpoint

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
succinate, and bisoprolol at their respective guideline-recommended target doses of 50, 200, and 10 mg/day) vs no β-blocker therapy	OPTIMIZE-HF registry (having a primary discharge diagnosis of HF), aged ≥65 years with EF ≥40% who were eligible for new discharge prescriptions of β-blockers	pairs) Up to 6 years (Median 2.2)	or HF rehospitalization Secondary: All-cause mortality, HF rehospitalization, and all-cause rehospitalization	during a median of 2.2 years of follow-up (HR, 1.03; 95% CI, 0.94 to 1.13; P=0.569). This association was homogeneous across various clinically relevant subgroups. Secondary: HRs for all-cause mortality and HF rehospitalization associated with a prescription for initiation of beta-blocker therapy were 0.99 (95% CI, 0.90 to 1.10; P=0.897) and 1.17 (95% CI, 1.03 to 1.34; P=0.014), respectively. The latter association lost significance when higher EF cutoffs of ≥45%, ≥50% and ≥55% were used.
Hannson et al[176] NORDIL Conventional therapy (diuretic, β-blocker or both) vs diltiazem 180 to 360 mg QD	BE, MC, OL, PRO, RCT Patients 50 to 74 years of age with DBP ≥100 mm Hg and previously untreated	N=10,881 4.5 years	Primary: Combined fatal and nonfatal stroke, fatal and nonfatal MI, other cardiovascular death Secondary: Fatal plus nonfatal stroke and fatal plus nonfatal MI	Primary: The primary endpoint occurred in 403 of the diltiazem patients and 400 of the diuretic/β-blocker patients (RR, 1.00; 95% CI, 0.87 to 1.15; P=0.97). Secondary: Rates of secondary endpoints were similar between the groups. Fatal plus nonfatal stroke occurred in 159 of the diltiazem patients and 196 of the diuretic/β-blocker patients (P=0.04). Fatal plus nonfatal MI occurred in 183 of the diltiazem patients and 157 of the diuretic/β-blocker patients (P=0.17). Other endpoints were not statistically different between the groups including cardiovascular death (P=0.41), all cardiac events (P=0.57) and congestive heart failure (P=0.42).
Messerli et al[177] β-blockers (atenolol, metoprolol or pindolol) vs	MA 10 RCTs lasting ≥1 year, which used as first line agents diuretics and/or β-	N=16,164 1 year	Primary: Cardiovascular morbidity and mortality, all-cause morbidity Secondary:	Primary: Diuretic treatment significantly reduced the odds for cardiovascular mortality by 25% (OR, 0.75; 95% CI, 0.64 to 0.87), while β-blockers did not reduce cardiovascular mortality (OR, 0.98; 95% CI, 0.78 to 1.23; P values not reported). Diuretic treatment significantly reduced the odds for all-cause mortality

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
diuretics (amiloride, chlorthalidone, HCTZ, HCTZ and triamterene [fixed-dose combination product], or thiazide)	blockers and reported morbidity and mortality outcomes in patients ≥60 years of age with HTN		Not reported	by 14% (OR, 0.86; 95% CI, 0.77 to 0.96), while β-blockers did not reduce all-cause mortality (OR, 1.05; 95% CI, 0.88 to 1.25; P values not reported). Secondary: Not reported
Wiysonge et al[178] β-blockers (atenolol, metoprolol, oxprenolol*, or propranolol) vs other antihypertensive therapies (i.e., placebo, diuretics, calcium channel blockers, or renin-angiotensin system inhibitors)	MA 13 RCTs evaluating patients ≥18 years of age with HTN	N=91,561 Duration varied	Primary: All-cause mortality Secondary: Stroke, CHD, cardiovascular death, total cardiovascular disease, adverse reactions	Primary: There was not a significant difference observed in all-cause mortality between β-blocker therapy and placebo (RR, 0.99; 95% CI, 0.88 to 1.11; P value not reported), diuretics (RR, 1.04; 95% CI, 0.91 to 1.19; P value not reported) or renin-angiotensin system inhibitors (RR, 1.10; 95% CI, 0.98 to 1.24; P value not reported). There was a significantly higher rate in all-cause mortality with β-blocker therapy compared to calcium channel blockers (RR, 1.07; 95% CI, 1.00 to 1.14; P=0.04). Secondary: There was a significant decrease in stroke observed with β-blocker therapy compared to placebo (RR, 0.80; 95% CI, 0.66 to 0.96). Also there was a significant increase in stroke with β-blocker therapy compared to calcium channel blockers (RR, 1.24; 95% CI, 1.11 to 1.40) and renin-angiotensin system inhibitors (RR, 1.30; 95% CI, 1.11 to 1.53), but there was no difference observed compared to diuretics (RR, 1.17; 95% CI, 0.65 to 2.09). CHD risk was not significantly different between β-blocker therapy and placebo (RR, 0.93; 95% CI, 0.81 to 1.07]), diuretics (RR, 1.12; 95% CI, 0.82 to 1.54), calcium channel blockers (RR, 1.05; 95% CI, 0.96 to 1.15) or renin-angiotensin system inhibitors (RR, 0.90; 95% CI, 0.76 to 1.06). The risk of total cardiovascular disease was lower with β-blocker therapy compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). The effect of β-blocker therapy on cardiovascular disease was significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				worse than that of calcium channel blockers (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from that of diuretics (RR, 1.13; 95% CI, 0.99 to 1.28) or renin-angiotensin system inhibitors (RR, 1.00; 95% CI, 0.72 to 1.3). There was a significantly higher rate of discontinuation due to side effects with β-blocker therapy compared to diuretics (RR, 1.86; 95% CI, 1.39 to 2.50) and renin-angiotensin system inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference compared to calcium channel blockers (RR, 1.20; 95% CI, 0.71 to 2.04). Actual side effects were not reported.
Lindholm et al[179] β-blocker therapy (atenolol, metoprolol, oxprenolol*, pindolol, or propranolol) vs other antihypertensive therapies (amiloride, amlodipine, bendro-flumethiazide*, captopril, diltiazem, enalapril, felodipine, HCTZ, isradipine, lacidipine, lisinopril, losartan, or verapamil) or placebo	MA 13 RCTs evaluating the treatment of primary HTN with a β-blocker as first-line treatment (in ≥50% of all patients in one treatment group) and outcome data for all-cause mortality, cardiovascular morbidity or both	N=105,951 2.1 to 10.0 years	Primary: Stroke, MI, all-cause mortality Secondary: Not reported	Primary: The RR of stroke was 16% higher with β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 1.04 to 1.30; P=0.009). The RR of stroke was the highest with atenolol (26% higher) compared to other non β-blockers (RR, 1.26%; 95% CI, 15 to 38; P<0.0001). The relative risk of MI was 2% higher for β- blocker therapy than for the comparator therapies (RR, 1.02; 95% CI, 0.93 to 1.12), which was not significant (P value not reported). The RR of all-cause mortality was 3% higher for β-blocker therapy than for the comparator therapies (RR, 1.16; 95% CI, 0.99 to 1.08; P=0.14). Secondary: Not reported
Freemantle et al[180]	MA (82 trials)	N=54,234	Primary: All-cause	Primary: The pooled random effects in short term trials demonstrated a mortality

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
β-blockers (acebutolol, alprenolol, atenolol, betaxolol, carvedilol, labetalol, oxprenolol*, pindolol, practolol*, propranolol, sotalol, timolol and xamoterol*) vs control (agents were not specified)	Patients with acute or past MI	6 to 48 months	mortality Secondary: Nonfatal reinfarction and withdrawal from treatment	rate of 10.5% (3,062 out of 29,260 patients) which is a 4% reduction compared to the controlled groups (OR, 0.96; 95% CI, 0.85 to 1.08). The pooled random effects in long term trials demonstrated a mortality rate of 9.7% (2415 out of 24974 patients) which is 23% reduction when compared to the controlled groups (OR, 0.77; 95% CI, 0.69 to 0.85). Individually, only four drugs achieved a statistically significant reduction in the death: propranolol (OR, 0.71; CI, 0.59 to 0.85]), timolol (OR, 0.59; CI, 0.46 to 0.77), metoprolol (OR, 0.80; CI, 0.66 to 0.96; and acebutolol (OR, 0.49; CI, 0.25 to 0.93). Secondary: A reduction in nonfatal re-infarctions of 0.9 events in every 100 (0.3 to 1.6) annually is suggested by this analysis; therefore about 107 patients would require treatment for one year to avoid one nonfatal reinfarction. Overall, 5,151 of 21,954 patients (23.5%) withdrew from treatment. with withdrawal occurring more often in the β-blocker groups. When comparing to placebo, the difference in annualized rate of withdrawal was 1.16 in 100 patients treated (1.16; 95% CI, 0.56 to 1.76).
Miscellaneous				
Schellenburg et al[181] Metoprolol 47.5 to 142.5 mg/day vs nebivolol 5 mg/day	DB, PRO, RCT Patients 18 to 65 years of age with the diagnosis of migraine with/ without aura, ≥1 year history, onset prior to 50 years of age, written record of attacks for the	N=38 30 weeks	Primary: Number of migraine attacks Secondary: Onset of action, duration of attacks, responder rate, severity, use of pain medication, migraine	Primary: There was not a significant difference in the frequency of migraine attacks observed between metoprolol and nebivolol (1.3±1.0 vs 1.6±1.5, respectively; P value not reported). Secondary: There was not a significant difference in any of the secondary endpoints observed between metoprolol and nebivolol (P values not reported). Use of acute pain medication decreased with both treatments, as well as accompanying symptoms. Both patient and physician evaluations of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	previous 3 months and ≥2 attack/month during screening		disability assessment, QOL score	disability and disease status were similarly favorable to the two treatments (P values not reported).
Silberstein et al[182] Propranolol ER 240 mg/day vs placebo	DB, MC, PC, RCT Patients with chronic migraine inadequately controlled (≥10 headaches/month) with topiramate (50 to 100 mg/day)	N=191 6 months	Primary: 28 day moderate to severe headache rate reduction at six months (weeks 16 to 24) compared to baseline (weeks -4 to 0) Secondary: Not reported	Primary: The six month reduction in moderate to severe 28 day headache rate and total 28 day headache rate for combination therapy vs topiramate was not significantly different (4.0 vs 4.5 days; P=0.57 and 6.2 vs 6.1; P=0.91). Secondary: Not reported
Tfelt-Hansen et al[183] Timolol 10 mg BID vs propranolol 80 mg BID vs placebo All patients entered a 4 week pretreatment period.	DB, PC, RCT, XO Patients 18 to 65 years of age with a history of 2 to 6 common migraine attacks per month	N=96 40 weeks	Primary: Frequency, duration and severity of attacks; number of responders (≥50% reduction in the frequency of attacks compared to baseline) Secondary: Frequency of attacks with associated symptoms, frequency of	Primary: Both timolol and propranolol decreased the frequency of attacks from baseline (P<0.01 for both). For severity of headache attacks, a small but significant reduction was observed with timolol (P<0.05 vs baseline). There was no effect on duration of attacks with either timolol or propranolol. The number of responders was significantly higher with timolol (n=44) and propranolol (n=48) compared to placebo (n=24; P<0.01 for both). Secondary: Both timolol and propranolol decreased the frequency of attacks associated with nausea or frequency of attacks associated with symptomatic therapy (P<0.01 for both vs baseline).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			attacks requiring relief medication	
Linde et al[184] Propranolol 60 to 320 mg/day vs placebo or another agent (calcium channel blockers, other β-blockers or other agent)	MA 26 randomized and quasi-randomized clinical trials of ≥4 weeks duration comparing clinical effects of propranolol with placebo or another drug in adult patients with migraine	N=5,072 4 to 30 weeks	Primary: Headache and migraine frequency Secondary: Not reported	Primary: Compared to placebo, propranolol showed a significant advantage in response to treatment with overall RR of response (“responder ratio”) of 1.94 (95% CI, 1.61 to 2.35). Compared to placebo, propranolol showed a significant advantage for the reduction of frequency of migraines with overall mean difference of -0.40 (95% CI, -0.56 to -0.24). Propranolol did not demonstrate a significantly greater response to treatment compared to calcium channel blockers with an overall responder ratio of 1.00 (95% CI, 0.92 to 1.09). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to calcium channel blockers with an overall mean difference of -0.02 (95% CI, 0.12 to 0.08). In the three trials comparing propranolol and nadolol, the overall responder ratio favored nadolol (responder ratio, 0.60; 95% CI, 0.37 to 0.97), but the results of the three trials were contradictory. In the three trials comparing propranolol and metoprolol, there was not a significant difference observed in the overall responder ratio between the two treatments (responder ratio, 0.78; 95% CI, 0.56 to 1.09). Propranolol did not demonstrate a significantly greater reduction in migraine frequency compared to other β-blockers with an overall mean difference of -0.01 (95% CI, 0.24 to 0.22). A quantitative MA was not performed on trials comparing propranolol to other drugs due to the great variety of comparator drugs used. One trial was significantly in favor of propranolol (vs amitriptyline), five with a trend in favor of propranolol, 11 showing no difference, two with a trend

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in favor of the comparator drug and one not interpretable; one of the two comparisons of propranolol alone and propranolol in combination with amitriptyline was classified as no difference, and the other as showing a trend in favor of the combination (P values not reported). Secondary: Not reported
Léauté-Labrèze et al[185] Propranolol (1 or 3 mg/kg/day, divided into two daily doses) vs placebo BID	DB, PC, RCT Patients 35 to 150 days of age with a proliferating infantile hemangioma requiring systemic therapy	N=460 24 to 96 weeks	Primary: Success (complete or nearly complete resolution of the target hemangioma) or failure of trial treatment at week 24 versus baseline according to centralized evaluation Secondary: Success or failure of trial treatment according to on-site assessments by the investigator at week 48 versus baseline	Primary: At the time of the interim analysis (188 patients completing 24 weeks of therapy), 2 of 25 patients (8%) receiving placebo had successful treatment at week 24, as compared with 4 of 41 patients (10%) receiving 1 mg/kg/day of propranolol for 3 months, 3 of 39 patients (8%) receiving 3 mg/kg/day for 3 months, 15 of 40 patients (38%) receiving 1 mg/kg/day for 6 months (P=0.004 for the comparison with placebo), and 27 of 43 patients (63%) receiving 3 mg/kg/day for 6 months (P<0.001 for the comparison with placebo). Overall, 61 of 101 patients (60%) assigned to the selected propranolol regimen and 2 of 55 patients (4%) assigned to placebo had successful treatment at week 24 (P<0.001). Improvement between baseline and week 5 (according to centralized assessment) occurred in 88% of patients assigned to the selected regimen and 5% of patients assigned to placebo (P<0.001). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, CR=controlled-release, ER=extended-release, QD=once daily, SR=sustained-release, TID=three times daily, XL=extended-release

Study design abbreviations: AC=active comparator, BE=blinded endpoint, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single blind, XO=cross over
Miscellaneous abbreviations: ACE inhibitor=angiotensin converting enzyme inhibitor, AF=atrial fibrillation, AIx=augmentation index, aPWV=aortic pulse wave velocity, ARB=angiotensin II receptor blocker, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CI=confidence interval, COPD=chronic obstructive pulmonary disease, DBP=diastolic blood pressure, ECG=electrocardiogram, ESRD=end stage renal disease, FEV1=forced expiratory volume in one second, GFR=glomerular filtration rate, HDL-C=high-density lipoprotein cholesterol, HR=hazard ratio, HTN=hypertension, LDL-C=low-density lipoprotein cholesterol, LVEF=left ventricular ejection fraction, MAP=mean arterial pressure, MI=myocardial infarction, NYHA=New York Heart Association, OR=odds ratio, PAD=peripheral arterial disease, pro-BNP= pro-B-type natriuretic peptide, PVD=peripheral vascular disease, QOL=quality of life, RMSSD=root mean square of successive RR intervals, RR=relative risk, SBP=systolic blood pressure, SDNN=standard deviation of the normal RR intervals, TC=total cholesterol, TG=triglyceride, TIA=transient ischemic attack, WHO=World Health Organization

Special Populations

Table 6. Special Populations[1-26,62]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Acebutolol	May require lower maintenance doses in the elderly (guidelines unavailable); doses above 800 mg/day should be avoided. Safety and efficacy in children have not been established.	Renal dose adjustment required; CrCl <50 mL/min (reduce dose by 50%), CrCl <25 mL/min (reduce dose by 75%).	Not reported	B	Yes; avoid use if breast feeding
Atenolol	Initiate at the low end of the dosing range in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment required; CrCl 15 to 35 mL/min (max dose 50 mg daily), CrCl <15 mL/min (max dose 25 mg daily).	Not reported	D	Yes; avoid use if breast feeding
Betaxolol	Use 5 mg once daily as initial therapy in the elderly. Safety and efficacy in children have not been established.	Renal dose adjustment required; severe (initial, 5 mg daily; max 20 mg daily).	No dosage adjustment required in hepatic dysfunction.	C	Yes; avoid use if breast feeding
Bisoprolol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment required; CrCl (initial 2.5 mg)	Hepatic dose adjustment required; hepatitis or cirrhosis (initial 2.5 mg)	C	Yes, avoid use if breast feeding
Carvedilol	No evidence of overall differences in safety or	No dose adjustment required for renal	Contraindicated in severe hepatic	C	Unknown; use with caution

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	dysfunction.	dysfunction. No dose adjustment required for other hepatic dysfunction.		
Esmolol	Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution
Labetalol	Consider a lower maintenance dosage in the elderly (100 to 200 mg twice a day). Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; avoid use if bread feeding
Metoprolol	Consider a lower initial dose in the elderly. Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Safety and efficacy in children have not been established	No dosage adjustment required.	Consider a lower initial dose in patients with hepatic dysfunction.	C	Yes; avoid use if bread feeding

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	(tartrate). FDA approved for use in children ages 6 to 17 (succinate).				
Nadolol	Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Safety and efficacy in children have not been established.	Renal dose adjustment required; CrCl 31 to 50 mL/min (increase dose interval to every 24 to 36 hours), CrCl 10 to 30 mL/min (increase dose interval to every 24 to 48 hours), CrCl <10 mL/min (increase dose interval to every 40 to 60 hours)	No dosage adjustment required.	C	Yes; avoid use if bread feeding
Nebivolol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment required; CrCl <30 mL/min (start with initial dose of 2.5 mg once daily, titrate up slowly if needed)	Hepatic dose adjustment required; moderate impairment (start with initial dose of 2.5 mg once daily) Has not been studied in severe hepatic dysfunction.	C	Yes; avoid use if bread feeding
Penbutolol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported.	Dose adjustment may be required (no guidelines available).	C	Yes; avoid use if bread feeding
Pindolol	Dose adjustment may be required in	No dosage adjustment is	Dose adjustment	B	Yes; avoid use if

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	elderly patients (no guidelines available). Safety and efficacy in children have not been established.	required.	may be required (no guidelines available).		bread feeding
Propranolol	Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Safety and efficacy in children have not been established (tablet, ER capsule, solution for IV injection) FDA approved for use in children less than age 1 (Hemangeol®).	No dosage adjustment required. Initiate dose at 80 mg once daily in patients with renal impairment (Innopran XL®)	Dose adjustment required (solution for injection); no guidelines available. Initiate dose at 80 mg once daily in patients with hepatic impairment (Innopran XL®)	C (Hemangeol® not intended for use in pregnancy)	Yes; avoid use if breast feeding
Sotalol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Decreased renal function associated with age may result in increased drug accumulation. Safety and efficacy in children have not been established.	Dose adjustment required (differs by product and indication, refer to specific drug package insert for dosing). Contraindicated in patients with CrCl <40 mL/min.	No dose adjustment required.	B	Yes; avoid use if breast feeding.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Timolol	Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Safety and efficacy in children have not been established.	No dose adjustment required.	Dose adjustment required (no guidelines available).	C	Yes; avoid use if breast feeding

CrCl=creatinine clearance, IV=intravenous

Adverse Drug Events

Table 7. Adverse Drug Events[1-26,62]

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Cardiovascular															
Angina	-	-	<2	-	1 to 6	-	-	-	-	-	-	-	a	-	a
Arrhythmia	-	-	<2	<1	-	-	-	-	<1	-	1 to 10	-	-	5	a
Arterial/vascular insufficiency	-	-	-	-	-	-	-	1	-	<1	-	-	a	-	-
Atrioventricular nodal disturbances	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Bradycardia	1 to 10	1 to 10	6 to 8	<1	2 to 10	-	<1	2 to 16	1 to 10	≤1	<1	≤2	6	13 to 16	1 to 10
Cardiogenic shock	-	-	-	-	-	-	-	a	-	-	-	-	a	-	-
Cerebrovascular accident	-	-	-	-	≤4	-	-	-	-	-	-	-	-	-	-
Chest pain	2	1 to 10	2 to 7	1 to 2	-	-	-	1	<1	≤1	-	3	2 to 4	3 to 16	-
Cold extremities	-	1 to 10	2	<1	-	-	-	1	1 to 10	-	<1	≤2	a	<1	a
Congestive heart failure	1 to 10	1 to 10	<2	<1	-	-	<1	1	1 to 10	-	1 to 10	<1	a	5	-
Edema	2	1 to 10	≤2	<1	5 to 6	-	≤2	-	1 to 10	-	<1	6	2	8	a
Flushing	-	-	-	<1	-	<1	1	-	-	-	-	-	-	-	-
Heart block	a	1 to 10	<2	-	≤4	-	<1	5	-	-	<1	≤2	-	-	a
Hypertension	-	-	<2	-	≤4	-	-	-	-	-	-	-	-	-	-
Hypotension	1 to 10	1 to 10	<2	<1	9 to 20	12 to 25	1 to 5	1 to 27	-	-	<1	≤2	a	6	a
Myocardial ischemia	-	-	-	-	-	-	-	-	-	<1	-	-	-	-	-
Orthostatic hypotension	-	-	-	<1	-	-	-	-	<1	-	-	-	-	-	-
Palpitations	a	-	2	<1	≤4	-	-	1	1 to 10	-	-	≤1	-	14	a
Peripheral circulation reduced	-	-	-	-	<1	-	-	-	1 to 10	-	-	-	-	3	-
Peripheral edema	-	-	-	-	1 to 7	-	-	1	-	1	-	-	-	-	-
Postural hypotension	-	-	-	-	≤4	-	-	-	-	-	-	-	-	-	-
Rhythm disturbance	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Shortness of breath	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-
Syncope	-	-	<2	<1	3 to 8	<1	<1	1	-	<1	-	-	-	-	-
Ventricular arrhythmias	a	-	-	-	-	-	-	-	-	-					
Central Nervous System															

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Abnormal dreams	2	-	<1	-	-	-	-	-	-	-	-	-	3	-	-
Amnesia	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Anxiety	1 to 10	-	-	<1	-	<1	-	a	-	-	-	-	-	4	a
Catatonia	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Cerebral vascular accident	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Concentration decreased	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	-
Confusion	-	1 to 10	-	<1	-	2	-	a	<1	-	<1	-	a	6	a
Depression	2	1 to 10	<1	<1	1 to 10	<1	-	5	1 to 10	-	1 to 10	-	1 to 3	4	a
Diaphoresis	-	-	<2	-	<1	-	-	-	-	-	-	-	-	-	-
Disorientation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Dizziness	6	1 to 10	-	<1	2 to 32	3	1 to 20	2 to 10	-	2 to 4	1 to 10	9	2 to 11	20	1 to 10
Drowsiness	-	-	-	-	-	-	-	-	>10	-	-	-	2	-	-
Emotional lability	-	-	-	-	-	-	-	-	-	-	-	-	a	<1	
Fatigue	11	1 to 10	3 to 10	6 to 8	4 to 24	-	1 to 11	1 to 10	-	-	1 to 10	8	3 to 17	20	1 to 10
Fever	-	-	<2	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Hallucinations	-	<1	<2	<1	-	-	-	a	<1	2 to 5	-	<1	a	-	a
Headache	6	1 to 10	-	<1	5 to 8	2	2	a	<1	-	1 to 10	-	1 to 9	8	-
Hyper/hypoesthesia	1 to 10	-	-	1 to 2	1 to 10	-	-	-	-	-	-	-	-	-	-
Insomnia	3	1 to 10	1 to 5	2 to 3	1 to 10	-	-	a	>10	6 to 9	<1	10	3 to 8	-	a
Lethargy	-	1 to 10	3	-	-	-	-	-	-	1	<1	-	4	-	-
Lightheadedness	-	-	-	-	-	<1	-	-	-	-	-	-	a	12	-
Malaise	-	-	<2	<1	1 to 10	-	-	-	-	-	-	-	-	-	-
Memory loss	-	-	<2	<1	<1	-	-	a	-	-	-	-	-	-	a
Mental impairment	-	1 to 10	-	-	-	-	-	-	-	-					
Nervousness	-	-	-	<1	<1	-	-	a	<1	-	-	7	2	-	a
Nightmares/ vivid dreams	-	1 to 10	-	-	<1	-	-	a	-	-	<1	5	a	-	a
Paresthesia	-	-	-	<1	-	<1	-	a	-	-					
Psychosis	-	<1	-	-	-	-	-	-	-	-	-	-	a	-	-
Sleep disturbance	-	-	-	<1	-	-	-	a	-	-	-	-	-	8	-
Somnolence	-	-	-	<1	1 to 10	3	3	a	-	-	-	-	a	-	a
Vertigo	-	-	-	<1	1 to 10	-	1 to 2	a	-	<1	-	-	a	<1	-

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Dermatologic															
Acne	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Alopecia	-	<1	<2	<1	<1	-	<1	a	-	-	-	-	a	<1	a
Cutaneous ulcers	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Dermatitis	-	-	-	<1	-	-	-	-	-	a	-	-	a	-	-
Eczema	-	-	-	<1	-	-	-	-	-	-	-	-	a	-	-
Erythema multiforme	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	-
Exfoliative dermatitis	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	-
Hyperkeratosis	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Nail changes	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Oculomucocutaneous reactions	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Photosensitivity	-	-	-	-	<1	-	-	a	-	-	-	-	-	<1	-
Pruritus	1 to 10	-	-	<1	<1	-	1	5	-	<1	-	1	a	<1	-
Pseudo pemphigoid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Psoriasiform rash	-	<1	-	<1	-	-	<1	-	-	-	-	-	a	-	a
Psoriasis (exacerbated)	-	-	-	<1	-	-	-	a	-	<1	-	-	-	-	a
Purpura	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Rash	2	-	1	<1	<1	-	1	5	-	≤1	-	-	0 to 2	5	a
Red crusted skin	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Scalp tingling	-	-	-	-	-	-	≤7	-	-	-	-	-	-	-	-
Skin necrosis after extravasation	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Stevens-Johnson syndrome	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	-
Sweating, excessive	-	-	-	-	-	-	-	a	-	-	-	≤2	2	<1	-
Systemic lupus erythematosus	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Toxic epidermal necrolysis	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	-
Ulcers	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Urticaria	-	-	-	-	-	-	<1	a	-	<1	-	-	a	5	a
Endocrine and Metobolic															
Diabetes (exacerbated)	-	-	<2	-	1 to 10	-	-	a	-	-	-	-	-	-	-
Gout	-	-	-	<1	1 to 10	-	-	-	-	-	-	-	-	-	-

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Hypoglycemia masked	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Libido decreased	-	-	-	-	-	-	-	a	-	-	-	-	-	-	a
Gastrointestinal															
Abdominal pain	1 to 10	-	-	<1	1 to 10	<1	-	a	-	1 to 10	-	-	1	-	-
Anorexia	a	-	<2	-	-	-	-	-	-	-	-	-	a	-	a
Constipation	4	1 to 10	<2	<1	-	<1	-	1	1 to 10	-	-	-	0 to 2	-	-
Cramping						-			-	-	-	-	a	-	-
Diarrhea	4	1 to 10	2	3 to 4	-	-	-	5	1 to 10	2 to 3	1 to 10	≤2	2 to 7	7	a
Dry mouth	-	-	-	-	-	<1	-	-	-	-	-	-	-	-	a
Dyspepsia	4	-	4 to 5	<1	-	<1	≤4	-	-	-	1 to 10	-	1 to 7	-	a
Epigastric distress	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Flatulence	3	-	-	-	-	-	-	1	-	-	-	-	4	2	-
Gastritis/gastric irritation	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Heartburn	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-
Ischemic colitis	-	-	-	-	-	-	-	-	-	-	<1	-	a	-	-
Melena	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Nausea	4	1 to 10	2 to 6	2	2 to 9	7	≤19	1	1 to 10	1 to 3	1 to 10	5	1 to 6	10	a
Pancreatitis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Peptic ulcer	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Periodontitis	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Retroperitoneal fibrosis	-	-	-	-	-	-	-	a	-	-	-	-	-	-	a
Stomach discomfort						-			1 to 10	-	-	-	a	3 to 6	-
Taste disorder	-	-	<2	<1	-	-	1	a	-	-	-	-	-	-	-
Vomiting	1 to 10	-	<2	1 to 2	1 to 6	1	≤3	a	1 to 10	<1	-	≤2	a	10	-
Weight gain	-	-	<2	<1	10 to 12	-	-	a	-	-	-	≤2	-	-	-
Xerostomia	a	-	<2	<1	<1	-	-	-	-	-	-	-	-	-	-
Genitourinary															
Cystitis	-	-	<2	<1	-	-	-	-	-	-	-	-	-	-	-
Diabetes insipidus	-	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Dysuria	1 to 10	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Ejaculatory failure	-	-	-	-	-	-	≤5	-	-	-	-	-	-	-	-
Hematuria	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Impotence	1 to 10	1 to 10	-	<1	1 to 10	-	1 to 4	a	-	<1	-	≤2	1	2	a

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Interstitial nephritis	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Libido decreased	-	-	<2	<1	<1	-	-	-	-	-	-	-	-	-	-
Micturition (frequency)	3	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Nocturia	1 to 10	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Oliguria	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Polyuria	-	-	-	<1	-	-	-	-	-	-	-	≤2	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Sexual ability decreased	-	-	-	-	-	-	-	-	>10	-	-	-	-	3	-
Urinary incontinence	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Urinary retention	a	-	-	-	-	<1	<1	-	-	-	-	-	-	-	-
Hematologic															
Agranulocytosis	-	-	-	-	<1	-	-	a	-	-	-	-	a	-	-
Anemia (aplastic/hemolytic)	-	-	<2	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Bleeding	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-
Claudication	-	-	-	-	-	-	-	a	-	-	-	-	-	-	a
Eosinophilia	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Leukopenia	-	-	-	<1	<1	-	-	-	<1	-	-	-	-	<1	-
Pancytopenia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Prothrombin decreased	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Purpura	-	-	<2	-	1 to 10	-	-	-	-	-	<1	-	a	-	-
Thrombocytopenia	-	<1	<2	<1	1 to 10	-	-	a	<1	1 to 10	<1	-	a	<1	-
Hepatic															
Cholestatic jaundice	-	-	-	-	<1	-	<1	-	-	-	-	-	-	-	-
Hepatic impairment	a	-	-	-	<1	-	<1	-	-	-	-	-	-	-	-
Hepatitis	-	-	-	-	-	-	<1	a	-	-	-	-	-	-	-
Increase liver enzymes	-	<1	-	-	-	-	-	-	-	<1	-	7	-	-	-
Transaminases increase	a	-	<2	<1	1 to 10	-	4	a	-	-	-	-	a	<1	-
Laboratory Test Abnormalities															
Alkaline phosphatase increased	a	-	-	-	-	-	-	a	-	-	-	<1	a	-	-
Hypercalcemia	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Hypercholesterolemia	-	-	<2	-	1 to 4	-	-	-	-	1 to 10	-	-	a	-	-
Hyperglycemia	-	-	<2	-	-	-	-	-	-	-	-	-	a	-	-
Hyperkalemia	-	-	<2	<1	1 to 10	-	-	-	-	-	-	-	-	-	-

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Hyperlipidemia	-	-	-	-	-	-	-	-	-	-	-	-	a	<1	-
Hypernatremia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hyperphosphatemia	-	-	-	-	3 to 6	-	-	-	-	-	-	-	-	-	-
Hypertriglyceridemia	-	-	-	<1	1	-	-	-	-	-	-	-	-	-	-
Hyperuricemia	-	-	<2	<1	1 to 10	-	-	-	-	1 to 10	-	<1	-	-	-
Hypervolemia	-	-	-	-	≤4	-	-	-	-	-	-	-	-	-	-
Hypoglycemia	-	-	<2	<1	1 to 10	-	-	-	-	-	<1	-	a	-	-
Hyponatremia	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Hypokalemia	-	-	<2	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	-	-	a	-	-	-	<1	-	-	-
Musculoskeletal															
Arthralgia	-	-	3 to 5	1 to 10	1 to 6	-	-	a	-	-	1 to 10	7	1	-	-
Arthritis	-	-	-	-	-	-	-	a	-	-	-	-	a	-	-
Arthropathy	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Asthenia	-	-	-	≤2	-	-	-	-	-	-	-	-	-	-	-
Back pain	1 to 10	-	-	<1	2 to 7	-	-	-	-	-	-	-	-	3	-
Carpal Tunnel syndrome	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Extremity pain	-	-	-	-	-	-	-	-	-	-	-	-	-	7	-
Joint pain	1 to 10	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Muscle cramps	-	-	<2	<1	1 to 10	-	-	-	-	-	-	3	-	-	-
Muscle pain	-	-	-	<1	-	-	-	a	-	-	-	10	-	-	-
Muscle spasm	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia	2	-	-	-	-	-	-	-	-	-	-	-	1	<1	-
Myasthenia gravis exacerbated	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
Myotonus	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Neuralgia	-	-	<2	-	<1	-	-	-	-	-	-	-	-	-	-
Paralysis	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	-
Paresthesia	-	-	-	-	-	-	≤5	-	-	1 to 10	-	3	a	4	a
Peripheral ischemia	a	-	-	-	-	1	-	-	-	-	-	-	-	-	-
Restlessness	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Tremor	-	-	<2	<1	-	-	-	-	-	-	-	-	-	-	-
Toxic myopathy	-	-	-	-	-	-	<1	-	-	-	-	-	-	-	-
Twitching	-	-	<2	<1	-	-	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	-	7 to 11	-	1	-	-	1 to 10	-	4	1	13	-

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Renal															
Blood urea nitrogen increased	-	-	-	<1	≤6	-	≤8	-	-	1 to 10	-	-	a	-	-
Creatinine increase	-	-	-	<1	1 to 10	-	-	-	-	-	-	-	-	-	-
Glycosuria	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-
Hematuria	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	-	-
Interstitial nephritis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Renal colic	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Renal failure/dysfunction	-	-	-	-	1 to 10	-	-	-	-	<1	-	-	-	-	-
Respiratory															
Asthma	-	-	-	<1	<1	-	-	-	-	-	-	-	-	2	-
Bronchitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	<1	<1	-	<1	1	1 to 10	<1	<1	-	a	-	a
Cough	1	-	<2	<1	5 to 8	-	-	-	-	-	<1	-	1	-	a
Dyspnea	4	<1	2	1 to 2	>3	-	2	1 to 3	<1	≤1	-	5	1 to 6	21	1 to 10
Eosinophilic pneumonitis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Interstitial pneumonitis	-	-	-	-	<1	-	-	-	-	-	-	-	-	-	-
Laryngospasm	-	-	-	-	-	-	-	-	-	-	-	-	a	-	-
Nasal congestion	-	-	-	-	1	-	1 to 6	-	-	-	-	-	-	-	a
Nasopharyngitis	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-
Pharyngitis	1 to 10	-	2	<1	-	-	-	-	-	-	-	-	a	-	-
Pleurisy	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pneumonitis	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	>3	-	-	-	-	<1	-	-	a	<1	a
Pulmonary granulomas	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Respiratory failure/distress	-	-	-	-	<1	-	-	-	-	-	-	-	a	-	a
Rhinitis	2	-	-	3 to 4	2	-	-	a	-	-	-	-	1	-	-
Sinus congestion	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
Upper respiratory infection	-	-	-	5	-	-	-	-	-	-	-	-	5	5 to 8	-
Wheezing	1 to 10	<1	-	-	-	-	-	1	-	-	-	≤2	a	-	-
Special Senses															
Abnormal/blurred vision	2	-	-	-	1 to 5	-	1	a	-	-	-	-	3	-	-
Blepharitis	-	-	<2	-	-	-	-	-	-	-					
Cataract	-	-	<2	-	-	-	-	-	-	-					

Adverse Event	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Conjunctivitis	1 to 10	-	-	-	-	-	-	-	-	-					
Dry eyes	1 to 10	-	-	-	-	-	-	a	-	-	-	-	-	-	a
Eye pain	1 to 10	-	-	<1	-	-	-	-	-	-	-	≤2	-	-	-
Hearing decreased	-	-	<2	<1	<1	-	-	-	-	-	-	-	-	-	-
Lacrimation, abnormal	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	<2	<1	<1	-	-	-	-	-	-	-	-	-	-
Visual disturbances	-	-	<2	<1	-	-	-	a	-	-	-	≤2	a	5	a
Other															
Allergy/allergic reaction	-	-	-	-	1 to 10	-	-	-	-	-	-	-	-	-	a
Anaphylactoid reaction	-	-	-	-	<1	-	<1	-	-	-	-	-	a	-	-
Angioedema	-	-	-	-	-	-	<1	-	-	<1	-	-	-	-	a
Cholecystitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cutaneous vasculitis	-	-	-	<1	-	-	-	-	-	-	-	-	-	-	-
Diaphoresis	-	-	-	-	-	-	≤4	-	-	-	-	-	-	-	-
Gangrene	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-
Hypersensitivity	-	-	-	-	-	-	<1	-	-	<1	-	-	-	-	-
Lupus syndrome	a	<1	-	-	-	-	<1	-	-	-	-	-	a	-	a
Metabolic acidosis	-	-	<2	-	-	-	-	-	-	-	-	-	-	-	-
Mesenteric arterial thrombosis	-	-	-	-	-	-	-	-	-	-	<1	-	-	-	-
Necrotizing angiitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Peyronie's disease	-	<1	<2	<1	-	-	<1	<1	-	-	-	-	a	-	a
Positive antinuclear antibody test	-	<1	5	<1	1 to 10	-	<1	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	-	-	-	a	-	-	-	-	-	-	-

a Percent not specified
- Event not reported

Contraindications

Table 8. Contraindications[1-26,62]

Contraindication	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Asthma, bronchial					a		a		a		a		a	a	
Asthma, bronchial or Chronic Obstructive Pulmonary Disease												a			a
Blood pressure less than 50/30 mmHg													a		
Bradycardia; severe, persistent	a							a †		a					
Bradycardia; severe, if no pacemaker is present					a										
Bradycardia; sinus		a	a						a		a		a	a	a
Bradycardia; sinus, severe				a		a	a					a			
Bradycardia; sinus (patient has hypertension and angina)								a *							
Cardiac failure, moderate to severe (patients with myocardial infarction)								a *							
Cardiogenic shock	a	a	a	a	a	a	a	a †	a	a	a	a	a	a	a
Conditions associated with severe and prolonged hypotension							a								
Creatine clearance <40 mL/minute														a	
Decompensated heart failure						a		a †		a			a		
Decompensated heart failure requiring intravenous inotropic therapy					a										
Heart Block, first-degree (PR interval 0.24 seconds or greater) (patients with myocardial infarction)								a *							
Heart Block, second- and third-degree	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Heart failure, uncontrolled														a	
Heart rate less than 45 beats/minute (patients with myocardial infarction)								a *							
Heart rate less than 80 beats/minute													a		
Hepatic impairment, Child-Pugh greater than B										a					
Hepatic impairment, severe					a										
Hypersensitivity to the drug or any component		a	a		a	a	a	a		a	a	a	a	a	a
Hypokalemia (serum potassium less than 4 mEq/L)														a	

Contraindication	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Infants weighing less than 2 kilograms													a		
Intravenous cardiodepressant calcium-channel antagonists administration in close proximity						a									
Long QT syndromes (acquired or congenital)														a	
Overt cardiac failure	a	a	a	a			a		a			a			a
Overt cardiac failure (patient has hypertension and angina)								a *							
Peripheral arterial circulatory disorders, severe (patients with hypertension and angina)								a *							
Pheochromocytoma													a		
Premature infants with corrected age less than 5 weeks													a		
Pulmonary Hypertension						a									
QT interval >450 milliseconds at baseline														a	
Sick sinus syndrome					a	a								a	
Sick sinus syndrome (patients with hypertension and angina)								a *							
Sick sinus syndrome (without functioning permanent pacemaker)								a †		a			a		
Systolic blood pressure less than 100 mmHg (patients with myocardial infarction)								a *							

*Contraindication relates to instant release tablet
†Contraindication relates to extended-release tablet

Black Box Warning for Tenormin® (atenolol) tablets[2]

WARNING
Cessation of Therapy with Tenormin®: Patients with coronary artery disease, who are being treated with TENORMIN®, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN® is planned, the patients should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN® be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN® therapy abruptly even in patients treated only for hypertension.

Black Box Warning for Lopressor® (metoprolol tartrate) tablet, solution for injection[10-11]

WARNING
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered LOPRESSOR®, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, LOPRESSOR® administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue LOPRESSOR® therapy abruptly even in patients treated only for hypertension

Black Box Warning for Toprol XL® (metoprolol succinate) extended-release tablet[12]

WARNING
Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL®, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 - 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TOPROL-XL® administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Warn patients against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TOPROL-XL® therapy abruptly even in patients treated only for hypertension

Black Box Warning for Corgard® (nadolol) tablet[13]

WARNING
Ischemic Heart Disease: Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered nadolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be reinstituted promptly, at least temporarily, and

WARNING
other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Black Box Warning for Inderal XL and InnoPran XL (propranolol) extended-release capsule[18,19]

WARNING
Cardiac Ischemia After Abrupt Discontinuation: Following abrupt discontinuation of therapy with beta-blockers, exacerbations of angina pectoris and myocardial infarction have occurred. When discontinuing chronically administered INDERAL XL®/INNOPRAN XL®, particularly in patients with ischemic heart disease, gradually reduce the dose over a period of 1-2 weeks and monitor the patients. If angina markedly worsens or acute coronary insufficiency develops, promptly resume therapy, at least temporarily and take other measures appropriate for the management of unstable angina. Warn patients against interruption or discontinuation of therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abrupt discontinuation of INDERAL XL®/INNOPRAN XL® therapy even in patient treated only for hypertension.

Black Box Warning for Betapace®, Betapace AF®, Sotylize® (sotalol), and sotalol injection[22-25]

WARNING
Life-threatening Proarrhythmia: To minimize the risk of induced arrhythmia, patients initiated or re-initiated on oral sotalol, and patients who are converted from intravenous sotalol to oral administration should be hospitalized in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring and calculations of creatinine clearance. · Sotalol can cause life-threatening ventricular tachycardia associated with QT interval prolongation. · Do not initiate sotalol therapy if the baseline QTc is longer than 450 ms. If the QT interval prolongs to 500 ms or greater, the dose must be reduced, the interval between doses prolonged, or the drug discontinued. · Adjust the dosing interval based on creatinine clearance.

Black Box Warning for timolol tablet[26]

WARNING
Exacerbation of ischemic heart disease following abrupt withdrawal: Hypersensitivity to catecholamines has been observed in patients withdrawn from β-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered timolol, particularly in patients with ischemic heart disease, gradually reduce the dosage over a period of one to two weeks and carefully monitor the patient. If angina markedly worsens or acute coronary insufficiency develops, reinstitute timolol administration promptly, at least temporarily, and take other measures appropriate for the management of unstable angina. Warn patients against interruption of discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue timolol therapy abruptly, even in patients treated only for hypertension.

Warnings/Precautions

Table 9. Warnings and Precautions[1-26,62]

Warning/Precaution	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
Abrupt Withdrawal: Exacerbation of Ischemic Heart Disease	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Anesthesia and Major Surgery: risk of excessive myocardial depression during general anesthesia may be enhanced and difficulty in restarting and maintaining the heart beat has been reported	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Bradycardia is common, use with caution.					a	a		a					a	a	
Bronchospastic Disease: patients should avoid use	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Cardiac Failure: β-adrenergic blockade may precipitate more severe failure	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Cardiac Failure (in patients with no history of cardiac failure): cardiac failure may result in with aortic or mitral valve disease or compromised left ventricular function due to continued depression of the myocardium	a	a	a	a			a	a				a			
Concomitant use of calcium channel blockers (verapamil or diltiazem): Bradycardia and heart block can occur and the left ventricular end diastolic pressure can rise.		a													
Deterioration of renal function has been reported					a										
Diabetes and Hypoglycemia: insulin-induced hypoglycemia may be potentiated, masked tachycardia may occur	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a
Electrolyte Disturbances (hypokalemia or hypomagnesemia)														a	
Hepatic injury, severe has been reported.							a								
Hyperkalemia; reported with use, increased risk with risk						a		a *		a					

Warning/Precaution	Acebutolol	Atenolol	Betaxolol	Bisoprolol	Carvedilol	Esmolol	Labetalol	Metoprolol	Nadolol	Nebivolol	Penbutolol	Pindolol	Propranolol	Sotalol	Timolol
factors such as renal impairment.															
Hypotension, increased risk for first 30 days of administration					a	a		a						a	
Hypovolemic patients; reflex tachycardia and increased risk of hypotension						a									
Infusion site reactions						a									
Intraoperative Floppy Iris Syndrome has been reported					a										
Metabolic Acidosis may be masked															
PHACE Syndrome, increased risk of stroke in patients with severe cerebrovascular abnormalities													a †		
Peripheral Circulatory Disorders may be aggravated						a									
Peripheral Vascular Disease: reduced cardiac output and can precipitate or aggravate the symptoms of arterial insufficiency	a		a		a			a *	a						
Pheochromocytoma, use an alpha-blocking agent before the beta-blocking agent					a		a	a *		a					
Pregnancy and fetal injury: can cause fetal harm when administered to a pregnant woman		a													
Prinzmetal's Variant Angina, use with caution					a	a									
Proarrhythmia; can provoke new or worsened ventricular arrhythmias													a		
Thyrotoxicosis: certain clinical signs (tachycardia) may be masked; discontinuation may precipitate a thyroid storm	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a

*Warning/precaution associated with extended-release tablet formulation
†Warning/precaution associated with solution (Hemangeol®) formulation

Drug Interactions

Table 10. Drug Interactions[1-26,186]

Generic Name	Interacting Medication or Disease	Potential Result
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Verapamil	May be synergistic or additive effects. Verapamil may inhibit oxidative metabolism of certain β-blockers. Additive QT interval prolongation is possible with sotalol.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Epinephrine	Nonselective β blockade allows α -receptor effects of epinephrine to predominate. Increasing vascular resistance leads to a rise in blood pressure and reflex bradycardia.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Sympatho-mimetics	Nonselective β-blockers may block the action of beta-agonists, potentially resulting in severe bronchospasm in asthmatics.
β-blockers (sotalol)	Bepridil	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Chloroquine	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and chloroquine are coadministered.
β-blockers (sotalol)	Class IA or IC Antiarrhythmic Agents	Class IA and IC antiarrhythmics and sotalol may cause additive pharmacologic and adverse cardiovascular effects when co- administered.
β-blockers (sotalol)	Dofetilide	The risk of cardiovascular toxicity, including torsades de pointes, may be increased by co-administration of dofetilide and sotalol. Pharmacologic effects of dofetilide and sotalol on electrical conduction of the heart may be additive.
β-blockers (sotalol)	Dronedarone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Droperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Fluconazole	Coadministration of fluconazole and sotalol may increase the risk of potentially fatal cardiac arrhythmias (torsades de pointes), especially in seriously ill patients and/or patients receiving high dose fluconazole.
β-blockers (sotalol)	Haloperidol	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Maprotiline	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Methadone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when sotalol is co-administered with methadone.
β-blockers (sotalol)	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and sotalol.
β-blockers (sotalol)	Pentamidine	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes,

Generic Name	Interacting Medication or Disease	Potential Result
		should be considered when sotalol is co-administered with pentamidine.
β-blockers (sotalol)	Perflutren	Additive QT interval prolongation may occur during coadministration of perflutren and sotalol.
β-blockers (sotalol)	Pheno-thiazines	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and phenothiazines are co-administered.
β-blockers (sotalol)	Phosphodiest erase type 5 Inhibitors	Phosphodiesterase type 5 inhibitors and sotalol may cause additive adverse effects when co-administered. Prolonged QT interval with the potential for cardiac arrhythmias may occur.
β-blockers (sotalol)	Pimozide	Sotalol and pimozide may cause additive adverse effects when co-administered. Cardiovascular toxicity, including torsades de pointes, may occur due to additive QT-interval prolongation.
β-blockers (sotalol)	Quinolones	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility.
β-blockers (sotalol)	Serotonin Receptor Antagonists Antiemetics	The risk of QT-interval prolongation and cardiac arrhythmias caused by serotonin receptor antagonist antiemetics may be increased by co-administration of sotalol.
β-blockers (sotalol)	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and sotalol.
β-blockers (sotalol)	Tyrosine Kinase Receptor Inhibitor	Additive QT interval prolongation is a possibility when tyrosine kinase receptor inhibitors are coadministered with sotalol.
β-blockers (sotalol)	Ziprasidone	Arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and ziprasidone are co-administered.
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Clonidine	B-blocker inhibition of β_2 receptor mediated vasodilation leaves peripheral α_2-receptor mediated vasoconstriction unopposed to clonidine stimulation.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Diltiazem	Additive AV nodal blockade may lead to synergistic bradycardia
β-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, metoprolol, nadolol, nebivolol,	Flecainide	Unknown mechanism. Combination may result in additive bradycardia and cardiac arrest

Generic Name	Interacting Medication or Disease	Potential Result
penbutolol, pindolol, propranolol, timolol)		
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Nonsteroidal Anti-inflammatory Drugs	NSAIDs may inhibit renal prostaglandin synthesis, allowing unopposed pressor systems to produce hypertension.
β-blockers (acebutolol, atenolol, betaxolol, carvedilol, metoprolol, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Quinazolines	Unknown mechanism. Additive vasodilation may increase risk of hypotension, specifically orthostatic hypotension. Generally occurs with the addition of prazosin to chronic β-blocker therapy, not β-blocker added to chronic prazosin therapy
β-blockers (bisoprolol, carvedilol, nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Insulin	β-blockers blunt sympathetic mediated responses to hypoglycemia.
β-blockers (atenolol, carvedilol, metoprolol, nadolol, pindolol, propranolol, sotalol)	Lidocaine	Reduced hepatic lidocaine metabolism and possibly a minor component of diminished hepatic blood flow.
β-blockers (bisoprolol, carvedilol, metoprolol, pindolol, propranolol, timolol)	Cimetidine	Cimetidine may reduce hepatic first-pass extraction, decrease liver blood flow, and inhibit hepatic metabolism of β-blockers.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Meglitinides	Unknown mechanism. Possible increase in hypoglycemic activity of meglitinides.
β-blockers (nadolol, penbutolol, pindolol, propranolol, sotalol, timolol)	Theophyllines	Pharmacologic antagonism. B-blockers may reduce the n-demethylation of theophylline.
β-blockers (atenolol, carvedilol, metoprolol, propranolol, timolol)	Quinidine	Oxidative metabolism of certain β-blockers may be inhibited by quinidine.
β-blockers (carvedilol, metoprolol, nebivolol, propranolol, timolol)	Terbinafine	Terbinafine inhibits CYP2D6 and may result in increased plasma concentrations of certain β-blockers.
β-blockers (carvedilol, metoprolol, propranolol, timolol)	Diphen-hydramine	Inhibition of CYP2D6-mediated β-blocker metabolism may decrease the metabolism of certain β-blockers resulting in excessive cardiovascular effects.

Generic Name	Interacting Medication or Disease	Potential Result
β-blockers (metoprolol, nebivolol, propranolol, timolol)	Serotonin Reuptake Inhibitors	Inhibition of CYP2D6 enzyme may decrease the metabolism of metoprolol resulting in excessive pharmacologic activity.
β-blockers (metoprolol, propranolol, sotalol)	Amiodarone	Additive pharmacologic effects of both drugs may result in severe bradycardia, hypotension, or cardiac arrest. Possible additive QT interval prolongation with sotalol and amiodarone.
β-blockers (pindolol, propranolol, sotalol)	Pheno-thiazines	Chlorpromazine may inhibit the first-pass hepatic metabolism of propranolol and increase its pharmacologic effects. Certain β-blockers may inhibit the metabolism of phenothiazines increasing the risk for cardiac side effects, including torsades de pointes.
β-blockers (carvedilol, metoprolol, propranolol)	Rifamycins (rifabutin, rifampin, rifapentine)	Possible decrease in oral bioavailability of carvedilol resulting in first-pass metabolism.
β-blockers (carvedilol, metoprolol, propranolol)	Thiamines	Hyperthyroidism appears to cause increased clearance of β-blockers with a high extraction ration. This may be the result of increased liver blood flow, first-pass metabolism and volume of distribution.
β-blockers (metoprolol, propranolol)	Hydralazine	Hydralazine increases systemic availability of some β-blockers, probably by transient increase in splanchnic blood flow and decreasing first-pass hepatic metabolism.
β-blockers (metoprolol, propranolol)	Propafenone	Propafenone increases plasma β-blocker level by decreasing first-pass metabolism and reducing systemic clearance. Both drugs are oxidized by the hepatic CYP450 system, and propafenone appears to inhibit the metabolism of the β-blocker.
β-blockers (atenolol)	Ampicillin	The bioavailability of atenolol may be decreased by impaired gastrointestinal absorption induced by ampicillin.
β-blockers (carvedilol)	Cyclosporine	Unknown mechanism. Carvedilol may increase plasma concentrations of cyclosporine and dose reduction may be required.
β-blockers (carvedilol)	Digoxin	Carvedilol may increase digoxin bioavailability. Possible additive depression of myocardial conduction and decreased renal tubular digoxin secretion.
β-blockers (labetalol)	Inhalation anesthetics	Additive myocardial depressant effects possibly resulting in excessive hypotension.
β-blockers (propranolol)	Mefloquine	Additive slowing of cardiac conduction possibly resulting in lengthening of the QT interval
β-blockers (propranolol)	Triptans	Unknown mechanism. Possible inhibition of triptan metabolism (monoamine oxidase-A) by propranolol resulting in enhanced pharmacologic effects and plasma concentrations.
β-blockers (sotalol)	Cisapride	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when cisapride is co-administered with sotalol.
β-blockers (sotalol)	H1 Antagonists	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered

Generic Name	Interacting Medication or Disease	Potential Result
		as a possibility when sotalol and H-1 antagonists are coadministered.
β-blockers (sotalol)	Iloperidone	Prolonged QT interval and cardiac arrhythmias are a potential when sotalol and iloperidone are used concomitantly.
β-blockers (sotalol)	Macrolides	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when sotalol and macrolides are coadministered.
β-blockers (sotalol)	Mefloquine	Co-administration of mefloquine and sotalol may cause cardiovascular toxicity, including electrocardiographic abnormalities such as QT interval prolongation
β-blockers (sotalol)	Mibefradil	Co-administration of sotalol and mibefradil may cause cardiovascular toxicity.
β-blockers (sotalol)	Paliperidone	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when paliperidone is co-administered with sotalol.
β-blockers (sotalol)	Propafenone	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered when sotalol and propafenone are coadministered.
β-blockers (sotalol)	Saquinavir	Coadministration of sotalol with saquinavir/ritonavir may be associated arrhythmias due to potential additive effects on prolongation of the QT interval.
β-blockers (sotalol)	Tricyclic Anti-depressants	The rare occurrence of arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when tricyclic antidepressants and sotalol are coadministered.

CYP=cytochrome P450 isoenzymes,

Dosage and Administration

Table 11. Dosing and Administration[1-26]

Generic Name	Adult Dose	Pediatric Dose	Availability
Acebutolol	Hypertension: Capsule: initial, 400 mg/day, twice daily dosing may be required for adequate control; maintenance, 200 to 1,200 mg/day in two divided doses; maximum, 1,200 mg/day Ventricular arrhythmias: Capsule: initial: 200 mg twice daily; maintenance, gradual increase until optimal response, usually 600 to 1,200 mg/day; maximum, 1,200 mg/day	Safety and efficacy in children have not been established.	Capsule: 200 mg 400 mg
Atenolol	Angina pectoris: Tablet: initial, 50 mg once daily; maintenance, if optimal response not	Safety and efficacy in children have not been established.	Tablet: 25 mg 50 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	achieved after one week, increase to 100 mg daily; maximum, 200 mg/daily Hypertension: Tablet: initial: 50 mg once daily; maintenance, if optimal response not achieved, increase dose to 100 mg once daily; maximum, 100 mg/day Myocardial infarction: Tablet: 50 mg twice daily, or 100 mg once daily for 6 to 9 days or until hospital discharge		100 mg
Betaxolol	Hypertension: Tablet: initial, 10 mg once daily; maintenance, if optimal response not seen after seven to 14 days, may increase the dose to 20 mg/day; maximum, 40 mg/day	Safety and efficacy in children have not been established.	Tablet: 10 mg 20 mg
Bisoprolol	Hypertension: Tablet: initial, 2.5 to 5 mg once daily; maintenance, if optimal control is not achieved, dose may be increased to 10 mg daily and again to 20 mg/day if needed; maximum, 20 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Carvedilol	Heart failure: Extended-release capsule: initial, 10 mg once daily; maintenance, if tolerated, double the dose at intervals of >14 days as needed; maximum, 80 mg once daily Tablet: initial, 3.125 mg twice daily; maintenance, if tolerated, double the dose at intervals of >14 days as needed up to 50 mg twice daily; maximum, 25 mg twice daily (patients ≤85 kg) or 50 mg twice daily (patients >85 kg) Hypertension: Extended-release capsule: initial, 20 mg once daily; maintenance, if tolerated, double the dose every seven to 14 days as needed; maximum, 80 mg once daily Tablet: initial, 6.25 mg twice daily; maintenance, if tolerated, double the dose every seven to 14 days as needed; maximum, 25 mg twice daily	Safety and efficacy in children have not been established.	Extended-release capsule (phosphate): 10 mg 20 mg 40 mg 80 mg Tablet: 3.125 mg 6.25 mg 12.5 mg 25 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Myocardial Infarction: Capsule ER: initial, 10 to 20 mg once daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 80 mg once daily Tablet IR: initial, 6.25 mg twice daily; maintenance: if tolerated, double the dose every 3 to 10 days as needed up to a maximum of 25 mg twice daily		
Esmolol	Supraventricular Tachycardia or Noncompensatory Sinus Tachycardia: Injection, IV solution: Step-wise dosing; optional loading dose 500 mcg/kg over one minute then 50, 100, or 150 mcg/kg/min for four minutes, may increase to 200 mcg/kg/min if needed. Maintenance infusions may continue for up to 48 hours. Intraoperative and Postoperative Tachycardia and/or Hypertension: Injection, IV solution: Immediate control, 1 mg/kg bolus over 30 seconds followed by 150 mcg/kg/min if needed, adjust rate as required; Gradual control, 500 mcg/kg bolus over one minute followed by 50 mcg/kg/min for four minutes; maximum maintenance doses, 200 mcg/kg/min (tachycardia) or 300 mg/kg/min (hypertension).	Safety and efficacy in children have not been established.	Injection: 10 mg/mL IV solution (Brevibloc®): 10 mg/mL 20 mg/mL
Labetalol	Hypertension: Injection, tablet: initial: 100 mg twice daily; maintenance, titrate by increments of 100 mg twice daily every two to three days, usual dose is 200 to 400 mg twice daily; larger doses may be administered three times daily to improve tolerability; maximum, doses of 1,200 to 2,400 mg/day have been used	Safety and efficacy in children have not been established.	Injection: 5 mg/mL Tablet: 100 mg 200 mg 300 mg
Metoprolol	Angina pectoris: Extended-release tablet: initial, 100 mg once daily; maintenance, gradually increase dose in weekly	Hypertension in children ≥6 years of age: Extended-release	Extended-release tablet (succinate): 25 mg 50 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	intervals; maximum, 400 mg/day Injection, tablet: initial, 100 mg/day in two divided doses; maintenance, gradually increase dose in weekly intervals, usual dose is 100 to 400 mg/day; maximum, 400 mg/day Heart failure: Extended-release tablet (NYHA Class II): initial, 25 mg/day; maintenance, double the dose every two weeks up to 200 mg/day or highest dose tolerated Extended-release tablet (NYHA Class >II): initial, 12.5 mg/day; maintenance, double the dose every two weeks up to 200 mg/day or highest dose tolerated Hypertension: Extended-release tablet: initial, 25 to 100 mg once daily; maintenance, gradually increase dose in weekly intervals up to 400 mg/day Injection, tablet: initial, 50 to 100 mg/day in single or divided doses; maintenance, gradually increase dose in weekly intervals, usual dose is 100 to 450 mg/day; maximum, 450 mg/day Myocardial infarction: Injection, tablet: initial, 100 mg twice daily; maintenance, 100 mg twice daily for at least three months	tablet: initial: 1 mg/kg once daily (maximum: 50 mg once daily); maintenance, adjust dose to optimal response up to 2 mg/kg or 200 mg/day; maximum, 2 mg/kg/day or 200 mg/day Safety and efficacy in children <6 years of age have not been established.	100 mg 200 mg Injection (tartrate): 5 mg/5 mL Tablet (tartrate): 25 mg 50 mg 100 mg
Nadolol	Angina pectoris: Tablet: initial, 40 mg once daily; maintenance, increase dose by 40 to 80 mg every three to seven days until optimal response; maximum, 240 mg/day Hypertension: Tablet: initial, 40 mg once daily; maintenance, increase dose gradually by 40 to 80 mg increments every seven to 21 days until optimal response; maximum, 320 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg 40 mg 80 mg
Nebivolol	Hypertension:	Safety and efficacy in	Tablet:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: initial: 5 mg once daily; maintenance, increase in two week intervals until optimal response; maximum, 40 mg/day	children have not been established.	2.5 mg 5 mg 10 mg 20 mg
Penbutolol	Hypertension: Tablet: initial, 20 mg once daily; maintenance, 20 mg once daily, usual dose 10 to 40 mg once daily; maximum, 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 20 mg
Pindolol	Hypertension: Tablet: initial, 5 mg twice daily; maintenance, after three to four weeks, may be increase by 10 mg/day increments as needed; maximum, 60 mg/day	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Propranolol	Angina pectoris: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may gradually increase dose in three to seven day increments up to 160 mg once daily or higher, usual dose is 160 mg daily; maximum, 320 mg/day Solution, tablet: maintenance, 80 to 320 mg/day administered in two, three or four divided doses; maximum, 320 mg/day Cardiac arrhythmias: Injection (ventricular arrhythmias): usual dose, 1 to 3 mg Solution, tablet (atrial fibrillation): maintenance, 10 to 30 mg in three to four divided doses before meals and at bedtime Essential tremor: Solution, tablet: initial, 40 mg twice daily; maintenance, usual dose is 120 mg/day; maximum, 320 mg/day Hypertension: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may titrate dose up to 120 mg/day or higher, usual dose is 120 to 160 mg/day; maximum, 640 mg/day Extended-release capsule (InnoPran	Infantile hemangioma: Solution (Hemangeol®): Initiate treatment at 5 weeks to 5 months; initial, 0.15 mL/kg (0.6 mg/kg) twice daily at least 9 hours apart; after one week increase to 0.3 mL/kg (1.1 mg/kg) twice daily; after another week increase the dose to 0.4 mL/kg (1.7 mg/kg) twice daily and maintain for six months, readjusting for weight changes Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than one year of age (Hemangeol®) Safety and efficacy in children have not been established (extended-release capsule, injection, oral solution [20 mg/5 mL, 40 mg/5 mL], tablet).	Extended-release capsule: 60 mg 80 mg 120 mg 160 mg Injection: 1 mg/mL Oral solution: 20 mg/5 mL 40 mg/5 mL Oral Solution (Hemangeol®): 4.28 mg/mL Tablet: 10 mg 20 mg 40 mg 60 mg 80 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	XL®): initial, 80 mg once daily at bedtime (around 10 pm); maintenance, may titrate dose up to 120 mg/day; maximum, 120 mg/day Solution, tablet: initial, 40 mg twice daily; maintenance, gradually increase the dose up to 640 mg/day divided into two to three doses, usual dose is 120 to 240 mg/day divided into two to three doses; maximum, 640 mg/day Hypertrophic subaortic stenosis: Extended-release capsule (Inderal LA®): maintenance, 80 to 160 mg once daily Solution, tablet: 20 to 40 mg three to four times daily before meals and at bedtime Migraine: Extended-release capsule (Inderal LA®): initial, 80 mg once daily; maintenance, may increase dose gradually up to 160 to 240 mg once daily, usual dose is 160 to 240 mg once daily; maximum, 240 mg/day Solution, tablet: initial, 80 mg daily in divided doses; maintenance, increase dose gradually up to 160 to 240 mg/day; maximum, 240 mg/day Myocardial Infarction: Solution, tablet: initial, 40 mg three times daily; maintenance, after one month, titrate up to 60 to 80 mg three times daily as tolerated, usual dose is 180 to 240 mg in divided doses; maximum, 240 mg/day Pheochromocytoma: Solution, tablet (operable tumors): 60 mg/day in divided doses for three days preoperatively as adjunct to alpha-adrenergic blockade Solution, tablet (inoperable tumors): 30 mg/day in divided doses as adjunct to alpha-adrenergic blockade		
Sotalol	Cardiac arrhythmias:	Safety and efficacy in	Injection:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Solution, tablet (Betapace AF®, Sotylize®; maintenance of normal sinus rhythm): initial, 80 mg twice daily; maintenance, increase dose gradually with three days between increments up to 120 mg twice daily; maximum, 160 mg twice daily Solution, tablet (Betapace®, Sotylize®; ventricular arrhythmias): initial, 80 mg twice daily; maintenance, increase dose gradually with three days between increments up to 120 to 160 mg twice daily; maximum, 480 to 640 mg/day	children have not been established.	150 mg/10 mL Oral Solution (Sotylize®): 5 mg/mL Tablet: 80 mg 120 mg 160 mg 240 mg
Timolol	Hypertension: Tablet: initial, 10 mg twice daily; maintenance, increase dose gradually in seven day increments up to 60 mg/day, usual dose is 20 to 40 mg/day; maximum, 60 mg/day divided into two doses Migraine: Tablet: initial, 10 mg twice daily; maintenance, may increase dose up to 30 mg/day; maximum, 30 mg/day divided into two doses Myocardial infarction: Tablet: 10 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg 20 mg

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily, (List in alphabetical order. No space needed before and after the "=". **Delete any abbreviation that is not used in the table above)**

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[29]	· Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients, unless contraindicated. · Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. · Patients with hypertension and established coronary artery disease (CAD) should be treated with blood pressure medication(s) as tolerated, including angiotensin converting enzyme (ACE) inhibitors and/or β-adrenergic antagonists (β-blockers) with the addition of other medications as needed to achieve blood pressure goals of <140/90 or <130/80 mm Hg for patients with chronic kidney disease or diabetes. · Long-acting calcium channel blocking agents or long-acting nitrates may be used if β-blockers are contraindicated. Immediate-release and short-acting

Clinical Guideline	Recommendations
	dihydropyridine calcium channel blockers can increase adverse cardiac events and should not be used. · Long-acting calcium channel blockers or long-acting nitrates may be used with β-blockers if initial treatment is not successful. · ACE inhibitors should be used indefinitely in patients with a left ventricular ejection fraction (LVEF) ≤40% and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated. · ACE inhibitors should also be used indefinitely in patients at lower risk (mildly reduced or normal LVEF in whom cardiovascular risk factors remain well controlled and revascularization has been performed), unless contraindicated. · Angiotensin II receptor blockers (ARBs) are recommended in patients with hypertension, those who have an indication for an ACE inhibitor and are intolerant to them, who have heart failure, or who have had a myocardial infarction (MI) and have a LVEF ≤40%. · ARBs may be considered in combination with an ACE inhibitor for heart failure due to left ventricular systolic dysfunction. · Aldosterone blockade is recommended in patients post-MI without significant renal dysfunction or hyperkalemia who are already receiving therapeutic doses of an ACE inhibitor and a β-blocker, have a LVEF ≤40% and have either diabetes or heart failure. · It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a MI, acute coronary syndrome or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. · Annual influenza vaccination is recommended in patients with cardiovascular disease.
European Society of Cardiology: **Guidelines on the Management of Stable Coronary Artery Disease (2013)**[30]	<u>General management of stable coronary artery disease (SCAD) patients</u> · The goal of management of SCAD is to reduce symptoms and improve prognosis. · The management of CAD patients encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. <u>General considerations for pharmacological treatments in SCAD patients</u> · Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention · It is recommended to educate patients about the disease, risk factors and treatment strategy. · It is indicated to review the patient's response soon after starting therapy. <u>Pharmacological treatments for angina/ischemia relief in SCAD patients</u> · Short-acting nitrates are recommended. · First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. · For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil* or ranolazine, according to heart rate, blood pressure, and tolerance. · For second-line treatment, trimetazidine* may be considered. · According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients. · In asymptomatic patients with large areas of ischaemia (>10%), ß-blockers should be considered.

Clinical Guideline	Recommendations
	· In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided. Pharmacological treatments for event prevention in SCAD patients · Low-dose aspirin daily is recommended in all SCAD patients. · Clopidogrel is indicated as an alternative in case of aspirin intolerance. · Statins are recommended in all SCAD patients. · It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). Treatment in patients with microvascular angina · It is recommended that all patients receive secondary prevention medications including aspirin and statins. · β-blockers are recommended as a first line treatment. · Calcium antagonists are recommended if β-blockers do not achieve sufficient symptomatic benefit or are not tolerated. · ACE inhibitors or nicorandil* may be considered in patients with refractory symptoms. · Xanthine derivatives (aminophylline, bamiphylline*) or non-pharmacological treatments such as neurostimulatory techniques may be considered in patients with symptoms refractory to the above listed drugs.
American College of Physicians/ American College of Cardiology Foundation/ American Heart Association/ American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/ Society of Thoracic Surgeons: **Management of Stable Ischemic Heart Disease (2012)**[31]	Medical therapy to prevent MI and death in patients with stable IHD · Aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications. · Treatment with clopidogrel is a reasonable option when aspirin in contraindicated. · Dipyridamole should not be used as antiplatelet therapy. · Beta-blocker therapy should be initiated and continued for three years in all patients with normal left ventricular (LV) function following MI or acute coronary syndromes. · Metoprolol succinate, carvedilol, or bisoprolol should be used for all patients with systolic LV dysfunction (ejection fraction ≤40%) with heart failure or prior MI, unless contraindicated. · ACE inhibitors should be prescribed in all patients with stable IHD who also have hypertension, diabetes, LV systolic dysfunction (ejection fraction ≤40%), and/or chronic kidney disease, unless contraindicated. · Angiotensin-receptor blockers (ARBs) are recommended for patients with stable IHD who have hypertension, diabetes, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors. · Patients should receive an annual influenza vaccine. Medical therapy for relief of symptoms in patients with stable IHD · Beta-blockers are recommended as initial therapy for relief of symptoms. · Calcium channel blockers or long-acting nitrates should be prescribed for relief of symptoms when β-blockers are contraindicated or cause unacceptable side effects. · Calcium channel blockers or long-acting nitrates, in combination with β-blockers, should be prescribed for relief of symptoms when initial treatment with β-blockers is unsuccessful. · Nitroglycerin or nitroglycerin spray should be used for immediate relief of

Clinical Guideline	Recommendations
	angina. · Ranolazine is a fourth-line agent reserved for patients who have contraindications to, do not respond to, or cannot tolerate β-blockers, calcium-channel blockers, or long-acting nitrates.
American College of Cardiology Foundation/American Heart Association: **2014 American Heart Association/ American College of Cardiology Foundation Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes (2014)**[32]	Early hospital care- standard medical therapies · Supplemental oxygen should be administered to patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) with arterial oxygen saturation <90%, respiratory distress, or other high risk features of hypoxemia. · Anti-ischemic and analgesic medications o Nitrates § Patients with NSTE-ACS with continuing ischemic pain should receive sublingual nitroglycerin (0.3 to 0.4 mg) every 5 minutes for up to three doses, after which an assessment should be made about the need for intravenous nitroglycerin. § Intravenous nitroglycerin is indicated for patients with NSTE-ACS for the treatment of persistent ischemia, heart failure, or hypertension. § Nitrates should not be administered to patients who recently received a phosphodiesterase inhibitor, especially within 24 hours of sildenafil or vardenafil, or within 48 hours of tadalafil. o Analgesic therapy § In the absence of contraindications, it may be reasonable to administer morphine sulphate intravenously to patients with NSTE-ACE if there is continued ischemic chest pain despite treatment with maximally tolerated anti-ischemic medications. § Nonsteroidal anti-inflammatory drugs (NSAIDs) (except aspirin) should not be initiated and should be discontinued during hospitalization due to the increased risk of major adverse cardiac event associated with their use o Beta-adrenergic blockers § Oral beta-blocker therapy should be initiated within the first 24 hours in patients who do not have any of the following: 1) signs of HF, 2) evidence of low-output state, 3) increased risk for cardiogenic shock, or 4) other contraindications to beta blockade (e.g., PR interval >0.24 second, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) § In patients with concomitant NSTE-ACS, stabilized heart failure, and reduced systolic function, it is recommended to continue beta-blocker therapy with one of the three drugs proven to reduce mortality in patients with heart failure: sustained-release metoprolol succinate, carvedilol, or bisoprolol. § Patients with documented contraindications to beta-blockers in the first 24 hours should be re-evaluated to determine subsequent eligibility. o Calcium channel blockers (CCBs) § In patients with NSTE-ACS, continuing or frequently recurring ischemia, and a contraindication to beta-blockers, a nondihydropyridine CCB (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction, increased risk for cardiogenic shock, PR interval >0.24 seconds, or second or third degree atrioventricular block without a cardiac pacemaker.

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	§ Oral nondihydropyridine calcium antagonists are recommended in patients with NSTE-ACS who have recurrent ischemia in the absence of contraindications, after appropriate use of beta-clockers and nitrates. § CCBs are recommended for ischemic symptoms when beta-blockers are not successful, are contraindicated, or cause unacceptable side effects. § Long-acting CCBs and nitrates are recommended in patients with coronary artery spasm. § Immediate-release nifedipine should not be administered to patients with NSTE-ACS in the absence of beta-blocker therapy. o Other anti-ischemic interventions § Ranolazine is currently indicated for treatment of chronic angina; however, it may also improve outcomes in NSTE-ACS patients due to a reduction in recurrent ischemia. o Cholesterol management § High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use. Treatment with statins reduces the rate of recurrent MI, coronary heart disease mortality, need for myocardial revascularization, and stroke. § It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation. · Inhibitors of renin-angiotensin-aldosterone system o ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated. o ARBs are recommended in patients with heart failure or myocardial infarction with LVEF <0.40 who are ACE inhibitor intolerant. o Aldosterone-blockade is recommended in patients post-MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta-blocker and have a LVEF <0.40, diabetes mellitus, or heart failure. · Initial antiplatelet/anticoagulant therapy in patients with definite or likely NSTE-ACS treated with an initial invasive or ischemia-guided strategy o Non-enteric coated, chewable aspirin (162 to 325 mg) should be given to all patients with NSTE-ACS without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 to 162 mg/day) should be continued indefinitely. o In patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel followed by a daily maintenance dose should be administered. o A $P2Y_{12}$ receptor inhibitor (clopidogrel or ticagrelor) in addition to aspirin should be administered for up to 12 months to all patients with NSTE-ACS without contraindications who are treated with an early invasive or ischemia-guided strategy. Options include: § Clopidogrel: 300 or 600 mg loading dose, then 75 mg daily. § Ticagrelor: 180 mg loading dose, then 90 mg twice daily. § It is reasonable to use ticagrelor in preference to clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo an early invasive or ischemia-guided strategy. § In patients with NSTE-ACS treated with an early invasive strategy

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	and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban. Percutaneous coronary intervention (PCI)- Antiplatelet and anticoagulant therapy · Antiplatelet agents o Patients already taking daily aspirin before PCI should take 81 to 325 mg non-enteric coated aspirin before PCI o Patients not on aspirin therapy should be given non-enteric coated aspirin 325 mg as soon as possible before PCI. o After PCI, aspirin should be continued indefinitely. o A loading dose of a $P2Y_{12}$ inhibitor should be given before the procedure in patients undergoing PCI with stenting. Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. o In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI. o In patients receiving a stent (bare metal or drug eluting) during PCI, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily. · Anticoagulant therapy o An anticoagulant should be administered to patients with NSTE-ACS undergoing PCI to reduce the risk of intracoronary and catheter thrombus formation. o Intravenous unfractionated heparin (UFH) is useful in patients with NSTE-ACS undergoing PCI. o Bivalirudin is useful as an anticoagulant with or without prior treatment with UFH. o An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at the time of PCI to patients with NSTE-ACS who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous enoxaparin dose eight to 12 hours before PCI. o If PCI is performed while the patient is on fondaparinux, an additional 85 IU/kg of UFH should be given intravenously immediately before PCI because of the risk of catheter thrombosis (60 IU/kg IV if a GP IIb/IIIa inhibitor used with UFH dosing based on the target-activated clotting time). o Anticoagulant therapy should be discontinued after PCI unless there is a compelling reason to continue. · Timing of CABG in relation to use of antiplatelet agents o Non-enteric coated aspirin (81 to 325 mg daily) should be administered preoperatively to patients undergoing CABG. o In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery and prasugrel for at least seven days before surgery. o In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding. o In patients referred for CABG, short-acting intravenous GP IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to

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	4 hours before surgery and abciximab for at least 12 hours before to limit blood loss and transfusion. Late hospital care, hospital discharge, and posthospital discharge care · Medications at discharge o Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with NSTE-ACS who do not undergo coronary revascularization, patients with incomplete or unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Titration of the doses may be required. o All patients who are post–NSTE-ACS should be given sublingual or spray nitroglycerin with verbal and written instructions for its use. o Before hospital discharge, patients with NSTE-ACS should be informed about symptoms of worsening myocardial ischemia and MI and should be given verbal and written instructions about how and when to seek emergency care for such symptoms. o Before hospital discharge, patients who are post–NSTE-ACS and/or designated responsible caregivers should be provided with easily understood and culturally sensitive verbal and written instructions about medication type, purpose, dose, frequency, side effects, and duration of use. o For patients who are post–NSTE-ACS and have initial angina lasting more than one minute, nitroglycerin (one dose sublingual or spray) is recommended if angina does not subside within three to five minutes; call 9-1-1 immediately to access emergency medical services. o If the pattern or severity of angina changes, suggesting worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or occurs at rest), patients should contact their clinician without delay to assess the need for additional treatment or testing. o Before discharge, patients should be educated about modification of cardiovascular risk factors. · Late hospital and post-hospital oral antiplatelet therapy o Aspirin should be continued indefinitely. The dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients. o In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. o In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y12 inhibitor therapy should be given for at least 12 months. · Combined oral anticoagulant therapy and antiplatelet therapy in patients with NSTE-ACS o The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. o Proton pump inhibitors should be prescribed in patients with NSTE-ACS with a history of gastrointestinal bleeding who require triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor.

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European Society of Cardiology: **Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2011)**[33]	Anti-ischemic drugs · Oral or intravenous nitrate treatment is indicated to relieve angina. Intravenous nitrates are recommended in patients with recurrent angina and/or signs of heart failure. · Patients on chronic β-blocker therapy admitted with acute coronary syndrome should be continued on β-blocker therapy if not in Killip class ≥III. · Oral β-blocker therapy is indicated in all patients with left ventricular dysfunction, unless contraindications are present. · Calcium channel blockers are recommended for relief of symptoms in patients already receiving nitrates and β-blocker therapy, and in patients with contraindications to β-blockade. · Calcium channel blockers are recommended in patients with vasospastic angina. · Intravenous β-blocker therapy at the time of admission should be considered for patients with stable hemodynamics with hypertension and/or tachycardia. · Nifedipine, or other dihydropyridines, are not recommended unless combined with β-blockers. Recommendations for drugs in secondary prevention · β-blockers are recommended in all patients with reduced left ventricular (LV) systolic function (LVEF ≤40%). · ACE inhibitors are indicated within 24 hours in all patients with LVEF ≤40% and in patients with heart failure, diabetes, hypertension, or CKD, unless contraindicated. · ACE inhibitors are recommended for all other patients to prevent recurrence of ischemic events, with preference given to agents and doses of proven efficacy. · ARBs are recommended for patients who are intolerant to ACE inhibitors, with preference given to agents and doses of proven efficacy. · Aldosterone blockade with eplerenone is indicated in patients after MI who are already being treated with ACE inhibitors and β-blockers and who have an LVEF ≤35% and either diabetes or heart failure, without significant renal dysfunction (serum creatinine >2.5 mg/dL for men and >2.0 mg/dL for women) or hyperkalemia. · Statin therapy with target LDL-C levels <70 mg/dL initiated early after admission is recommended.
American College of Cardiology/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[34]	Routine medical therapies: β-blockers · Oral β-blockers should be initiated within the first 24 hours in patients with an ST-segment elevation myocardial infarction (STEMI) who do not have any of the following: 1) signs of heart failure, 2) evidence of a low-output state, 3) increased risk of cardiogenic shock, 4) other contraindications to use of oral β-blockers (e.g., PR interval >24 seconds, second or third degree heart block, active asthma, reactive airway disease). · β-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use. · Patients with initial contraindications to the use of β-blockers in the first 24 hours after STEMI should be re-evaluated to determine their subsequent eligibility. · It is reasonable to administer intravenous β-blockers at the time of

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	presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia. Routine medical therapies: Renin-Angiotensin-Aldosterone System Inhibitors · An angiotensin-converting enzyme (ACE) inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or ejection fraction (EF) ≤40%, unless contraindicated. · An angiotensin receptor blocker (ARB) should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors. · An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and β-blocker and who have an EF ≤40% and either symptomatic heart failure or diabetes. Routine medical therapies: Lipid management · High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use. · It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.
European Society of Cardiology: **Management of Acute Myocardial Infarction in Patients Presenting with ST-segment Elevation (2012)**[35]	Routine therapies in the acute, subacute and long term phase of STEMI · Active smokers with STEMI must receive counseling and be referred to a smoking cessation program. · Each hospital participating in the care of STEMI patients must have a smoking cessation protocol. · Exercise-based rehabilitation is recommended. · Antiplatelet therapy with low dose aspirin (75 to 100 mg) is indicated indefinitely after STEMI. · In patients intolerant to aspirin, clopidogrel is indicated as an alternative. · Dual antiplatelet therapy with a combination of aspirin and prasugrel or aspirin and ticagrelor is recommended (over aspirin and clopidogrel) in patients treated with PCI. · Dual antiplatelet therapy with aspirin and an oral ADP receptor antagonist must be continued for up to 12 months after STEMI, with a strict minimum of 1 month for patients receiving bare metal stent and 6 months for patients receiving drug-eluting stent. · In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. · In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy. · If patients require triple antithrombotic therapy, combining dual antiplatelet therapy and oral anticoagulant, e.g. because of stent placement and an obligatory indication for oral anticoagulation, the duration of dual antiplatelet therapy should be minimized to reduce bleeding risk. · In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk. · Dual antiplatelet therapy should be used up to 1 year in patients with STEMI who did not receive a stent. · Gastric protection with a proton pump inhibitor should be considered for the duration of DAPT therapy in patients at high risk of bleeding. · Oral treatment with β-blockers should be considered during hospital stay and

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	continued thereafter in all patients without contraindications. · Oral treatment with β-blockers is indicated in patients with heart failure or left ventricular dysfunction. · Intravenous β-blockers must be avoided in patients with hypotension or heart failure. · Intravenous β-blockers should be considered at the time of presentation in patients without contraindications, with high blood pressure, tachycardia, and no signs of heart failure. · A fasting lipid profile must be obtained in all STEMI patients, as soon as possible after presentation. · It is recommended to initiate or continue high dose statins early after admission in all STEMI patients without contraindication or history of intolerance, regardless of initial cholesterol values. · Reassessment of LDL-cholesterol should be considered after 4–6 weeks to ensure that a target value of ≤70 mg/dL has been reached. · Verapamil may be considered for secondary prevention in patients with absolute contraindications to β-blockers and no heart failure. · ACE inhibitors are indicated starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes or an anterior infarct. · An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure or LV systolic dysfunction, particularly those who are intolerant to ACE inhibitors. · ACE inhibitors should be considered in all patients in the absence of contraindications. · Aldosterone antagonists, e.g. eplerenone, are indicated in patients with an ejection fraction ≤40% and heart failure or diabetes, provided no renal failure or hyperkalemia.
National Institute for Health and Clinical Excellence: **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2013)**[36]	<u>Drug therapy</u> · Offer all people who have had an acute MI treatment with the following drugs: o Angiotensin-converting enzyme (ACE) inhibitor. o Dual antiplatelet therapy (aspirin plus a second agent). o β-blocker. o Statin. · Ensure that a clear management plan is available to the person who has had an MI and is also sent to their provider. · Offer all people who have had an MI an assessment of bleeding risk at their follow-up appointment. · Offer an assessment of left ventricular (LV) function to all people who have had an MI. <u>ACE inhibitors</u> · Offer people who present acutely with an MI an ACE inhibitor as soon as they are hemodynamically stable. Continue the ACE inhibitor indefinitely. · Titrate the ACE inhibitor dose upwards at short intervals (for example, every 12 to 24 hours) before the person leaves hospital until the maximum tolerated or target dose is reached. If it is not possible to complete the titration during this time, it should be completed within 4 to 6 weeks of hospital discharge. · Do not offer combined treatment with an ACE inhibitor and an angiotensin II receptor blocker (ARB) to people after an MI, unless there are other reasons to use this combination.

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	· Renal function, serum electrolytes and blood pressure should be measured before starting an ACE inhibitor or ARB and again within 1 or 2 weeks of starting treatment. More frequent monitoring may be needed in patients who are at increased risk of deterioration in renal function. · Offer an ACE inhibitor to people who have had an MI more than 12 months ago. Titrate to the maximum tolerated or target dose (over a 4 to 6 week period) and continue indefinitely. An ARB may be used as alternative therapy. Antiplatelet therapy · Offer aspirin to all people after an MI and should be continued indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. Clopidogrel should not be offered as first-line monotherapy after a MI. · Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely. · For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment. · Special considerations should be made for people with dyspepsia. · After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI). · Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent. · Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent. · Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery. · Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and topped dual antiplatelet therapy or had an MI more than 12 months ago). Antiplatelet therapy in people with an indication for anticoagulation · Take bleeding risk, thromboembolic risk and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation. · Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery. · Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation. · Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI. · Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI. · After 12 months since the MI, continue anticoagulation and take into

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	consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes. · Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who otherwise need anticoagulation, who have had an MI. · Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it. Beta-blockers · After an acute MI, all patients without left ventricular systolic dysfunction or with left ventricular systolic dysfunction should be offered treatment with a β-blocker. · β-blockers should be continued indefinitely after an acute MI. · After a proven MI in the past, asymptomatic patients with preserved left ventricular function should not routinely be offered a β-blocker unless they are at risk for further cardiovascular events or other compelling indications exist. Calcium channel blockers · Do not routinely offer calcium channel blockers to reduce cardiovascular risk after an MI. · If beta-blockers are contraindicated or need to be discontinued, diltiazem or verapamil may be considered for secondary prevention in patients without pulmonary congestion or left ventricular systolic dysfunction. Aldosterone antagonists in patients with heart failure and left ventricular dysfunction · For patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, initiate treatment with an aldosterone antagonist licensed for post-MI treatment within 3 to 14 days of the MI, preferably after ACE inhibitor therapy. · Monitor renal function and serum potassium before and during treatment with an aldosterone antagonist.
American College of Cardiology/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[37]	Treatment of Stage A heart failure (HF) · Hypertension and lipid disorders should be controlled in accordance with guidelines to lower the risk of HF. (Level of Evidence (LoE): A) · Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents, should be controlled or avoided. (LoE: C) Treatment of Stage B heart failure · In patients with a history of MI and reduced EF, ACE inhibitors or ARBs should be used to prevent HF. (LoE: A) · In patients with MI and reduced EF, evidence-based beta blockers (using one of three proven to reduce mortality [i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate]) should be used to prevent HF. (LoE: B) · In patients with MI, statins should be used to prevent HF. (LoE: A)

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	· ACE inhibitors and beta-blockers should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (LoE: A and C, respectively) · Blood pressure should be controlled to prevent symptomatic HF. (LoE: A) · Nondihydropyridine calcium channel blockers may be harmful in patients with low LVEF. (LoE: C) Pharmacological treatment for Stage C HFrEF · Recommendations for patients in Stages A and B are recommended where appropriate for patients in Stage C. (LoE: A, B, and C as appropriate) · Diuretics are recommended in patients with HFrEF who have evidence of fluid retention, unless contraindicated, to improve symptoms. (LoE: C) · ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality. ARBs are recommended as alternative therapy in ACE inhibitor intolerant patients. (LoE: A) · Use of one of the three beta-blockers proven to reduce mortality is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated, to reduce morbidity and mortality. (LoE: A) · Aldosterone receptor antagonists are recommended in patients with NYHA class II–IV HF and who have LVEF of ≤35%, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m^2), and potassium should be <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency. (LoE: A) · The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated. (LoE: A) · Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. (LoE: B) · Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age) should receive chronic anticoagulant therapy. (LoE: A) · Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use. (LoE: A) · Calcium channel blockers are not recommended as routine treatment for patients with HFrEF. (LoE: A) Pharmacological treatment for Stage C HFpEF · Blood pressure should be controlled according to published clinical practice guidelines. (LoE: B) · Diuretics should be used for relief of symptoms due to volume overload. (LoE: C) · The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. (LoE: C)

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	Treatment of Stage D (advanced/refractory) HF · Fluid restriction (1.5 to 2 L/d) is reasonable, especially in patients with hyponatremia, to reduce congestive symptoms. (LoE: C) · Until definitive therapy (e.g., coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance. (LoE: C) · Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D HF refractory to medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation. (LoE: B) · Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF. (LoE: B)
Heart Failure Society of America: **Heart Failure Society of America 2010 Comprehensive Heart Failure Practice Guidelines (Executive Summary) (2010)**[38]	Patients with left ventricular systolic dysfunction · ACE inhibitors should be used in all patients with a LVEF ≤40%, unless otherwise contraindicated. · ARBs may be used in patients who are intolerant to ACE inhibitors. Hydralazine and a nitrate may be used in patients intolerant to ACE inhibitors and ARBs, or in whom such therapy is contraindicated. · The combination of an ACE inhibitor and a β-blocker is recommended in all patients with a LVEF ≤40%. · The routine use of an ARB with a combination of an ACE inhibitor and β-blocker in patients who have had a MI and have left ventricular dysfunction is not recommended. · The addition of an ARB can be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. · Individual ARBs may be considered as initial therapy (instead of an ACE inhibitor) in patients with heart failure who have had a MI and in patients with chronic heart failure and systolic dysfunction. · ARBs are recommended in patients who cannot tolerate ACE inhibitors due to cough. The combination of hydralazine and an oral nitrate may be considered in such patients not tolerating ARB therapy. · Patients intolerant to ACE inhibitors from hyperkalemia or renal insufficiency are likely to experience the same side effects with ARBs. In these cases, the combination of hydralazine and an oral nitrate should be considered. · ARBs should be considered in patients experiencing angioedema while on ACE inhibitors based on their underlying risk and with recognition that angioedema has been reported infrequently with ARBs. The combination of hydralazine and oral nitrates may be considered in such patients not tolerating ARB therapy. · A combination of hydralazine and an oral nitrate is recommended in African American patients with heart failure and reduced left ventricular ejection fraction (LVEF) who are on a standard regimen of an ACE inhibitor (or ARB) and a β-blocker. · A combination of hydralazine and an oral nitrate may be considered in non–African American patients with heart failure and reduced LVEF who are

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	symptomatic despite optimization of standard therapy. · Administration of an aldosterone antagonist is recommended for patients with New York Heart Association (NYHA) class IV (or class III, previously class IV) heart failure from reduced LVEF (<35%) while receiving standard therapy, including diuretics. · Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical heart failure signs and symptoms or history of diabetes mellitus, and an LVEF <40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker. · The triple combination of an ACE inhibitor, an ARB, and an aldosterone antagonist is not recommended because of the high risk of hyperkalemia. Patients with hypertension and symptomatic left ventricular dysfunction with left ventricular dilation and low LVEF · ACE inhibitors, ARBs, β-blockers, aldosterone inhibitors, and isosorbide dinitrate/hydralazine in various combinations (with a loop diuretic if needed) are recommended. · If blood pressure remains >130/80 mm Hg, a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) may be considered or other antihypertensive medication doses increased. Managing heart failure in special populations · The combination of hydralazine/isosorbide dinitrate is recommended for African American women with moderate to severe heart failure symptoms who are on background neurohormonal inhibition. · A combination of hydralazine and isosorbide dinitrate is recommended as part of standard therapy in addition to β-blockers and ACE-inhibitors for African Americans with left ventricular systolic dysfunction and NYHA class II-IV heart failure. · As in all patients, but especially in the elderly, careful attention to volume status, the possibility of symptomatic cerebrovascular disease and the presence of postural hypotension are recommended during therapy with ACE inhibitors, β-blockers and diuretics. Patients with heart failure and preserved LVEF · ACE inhibitors or ARBs should be considered in this patient population. · ACE inhibitors should be considered in patients with heart failure and symptomatic atherosclerotic cardiovascular disease or diabetes and at least one other risk factor. ARBs may be used in patients who are intolerant to ACE inhibitors. · Beta blocker treatment is recommended in patients with HF and preserved LVEF who have prior MI, hypertension, or AF. · Calcium channel blockers should be considered in patients with heart failure and preserved LVEF who have atrial fibrillation requiring ventricular rate control and intolerance to β-blockers (consider diltiazem or verapamil), symptom-limiting angina, or hypertension. · Diuretic therapy is recommended in all patients with heart failure and clinical evidence of volume overload, including those with preserved LVEF. · Treatment may begin with either a thiazide or loop diuretic. In more severe volume overload or if response to a thiazide is inadequate, treatment with a loop diuretic should be implemented.

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	· Excessive diuresis, which may lead to orthostatic changes in blood pressure and worsening renal function, should be avoided. Patients with heart failure and CAD · Calcium channel blockers should be considered in patients who have angina despite optimization of β-blocker and nitrates. Amlodipine and felodipine are preferred in patients with decreased systolic function. Patients with heart failure and hypertension · Patients with left ventricular hypertrophy or left ventricular dysfunction without left ventricular dilation should be treated to a goal blood pressure of <130/80 mm Hg. Treatment with several drugs may be necessary, including an ACE inhibitor (or ARB), a diuretic and a β-blocker or calcium channel blocker. · Patients with asymptomatic left ventricular dysfunction and left ventricular dilation and a reduced ejection fraction should receive an ACE inhibitor and a β-blocker. If blood pressure remains elevated (>130/80 mm Hg), the addition of a diuretic is recommended, followed by a calcium channel blocker or other antihypertensive agent. · If blood pressure remains >130/80 mm Hg, then the addition of a thiazide diuretic is recommended, followed by a dihydropyridine calcium channel blocker (e.g., amlodipine or felodipine) or other antihypertensive drugs. Patients at risk for development of heart failure · ACE inhibitors are recommended in patients who are at risk for the development of heart failure including patients with CAD, peripheral vascular disease, stroke, diabetes and another major risk factor, and patients with diabetes who smoke and have microalbuminuria. Patients with asymptomatic heart failure and reduced LVEF · ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). · ARBs may be used in patients who are intolerant to ACE inhibitors. · Routine use of a combination of ACE inhibitors and ARBs is not recommended. · β-blocker therapy should be considered. Patients with heart failure and ischemic heart disease · ACE inhibitor therapy is recommended in all patients with either reduced or preserved LVEF after a MI. · Beta blockers are recommended for the management of all patients with reduced LVEF or post-MI. · ACE inhibitor and β-blocker therapy should be initiated early (<48 hours) during hospitalization in hemodynamically stable patients who are post-MI with reduced LVEF or heart failure. · Calcium channel blockers may be considered in patients with HF who have angina despite the optimal use of beta blockers and nitrates. Managing heart failure in the elderly, women and African Americans · Standard regimens of ACE inhibitors and β-blockers are recommended in elderly patients with heart failure. · ACE inhibitor and β-blocker therapy are recommended in all women with

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	heart failure and left ventricular systolic dysfunction. · ACE inhibitor and β-blocker therapy are recommended in all African American patients with heart failure and left ventricular systolic dysfunction. ARBs may be substituted in patients who are intolerant to ACE inhibitors. Heart failure in patients with reduced ejection fraction · ACE inhibitors are recommended in asymptomatic patients with reduced LVEF (<40%). · ARBs may be used in patients who are intolerant to ACE inhibitors. · β-blockers shown to be effective in clinical trials of patients with heart failure are recommended for patients with a LVEF ≤40%. · The combination of a β-blocker and an ACE inhibitor is recommended as routine therapy for asymptomatic patients with a LVEF ≤40%. The evidence is stronger in patients with a history of MI. · β-blocker therapy is recommended for patients with a recent decompensation of heart failure after optimization of volume status and successful discontinuation of intravenous diuretics and vasoactive drugs. Whenever possible, β-blocker therapy should be initiated in the hospital setting at a low dose prior to discharge of stable patients. · β-blocker therapy is recommended in the great majority of patients with heart failure and reduced LVEF, even if there is concurrent diabetes, chronic obstructive pulmonary disease or peripheral vascular disease. Caution may be warranted in these patients. · It is recommended that β blockade be initiated at low doses and uptitrated gradually. · It is recommended that β-blocker therapy be continued in most patients experiencing a symptomatic exacerbation of heart failure during chronic maintenance treatment, unless they develop cardiogenic shock, refractory volume overload or symptomatic bradycardia. · The routine use of an ARB is not recommended in addition to an ACE inhibitor and a β-blocker in patients with a recent acute MI and reduced LVEF. · The addition of an ARB should be considered in patients with heart failure due to reduced LVEF who have persistent symptoms or progressive worsening despite optimized therapy with an ACE inhibitor and a β-blocker. · Administration of an aldosterone antagonist is recommended for patients with NYHA class IV (or class III, previously class IV) HF from reduced LVEF (<35%) while receiving standard therapy, including diuretics. · Diuretic therapy is recommended to restore and maintain normal volume status in patients with clinical evidence of fluid overload, generally manifested by congestive symptoms or signs of elevated filling pressures. Loop diuretics rather than thiazide-type diuretics are typically necessary to restore normal volume status in patients with heart failure. · The initial dose of diuretic may be increased as necessary to relieve congestion, and restoration of normal volume status may require multiple adjustments, especially in patients with severe fluid overload evidenced by massive edema or ascites. After a diuretic effect is achieved with loop diuretics (short acting), increasing administration frequency to twice or even three times/day will provide more diuresis with less physiologic perturbation than larger single doses. · Oral torsemide may be considered in patients in whom poor absorption of oral medication or erratic diuretic effect may be present. Particularly in

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	patients with right-sided heart failure and refractory fluid retention despite high doses of other loop diuretics. · Intravenous administration of diuretics may be necessary to relieve congestion. · Diuretic refractoriness may represent patient nonadherence, a direct effect of diuretic use on the kidney or progression of underlying cardiac dysfunction. · Addition of chlorothiazide or metolazone, once or twice daily, to loop diuretics should be considered in patients with persistent fluid retention despite high dose loop diuretic therapy. Chronic daily use should be avoided if possible because of the potential for electrolyte shifts and volume depletion. These drugs may be used periodically (every other day or weekly) to optimize fluid management. Metolazone will generally be more potent and much longer acting in this setting and in patients with chronic renal insufficiency, so administration should be adjusted accordingly. Volume status and electrolytes must be monitored closely when multiple diuretics are used. · Careful observation for the development of side effects is recommended in patients treated with diuretics, especially when high doses or combination therapy are used. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. · Patients requiring diuretic therapy to treated fluid retention associated with heart failure generally require chronic treatment, although often at lower doses than those required initially to achieve diuresis. Decreasing or discontinuing therapy may be considered in patients experiencing significant improvement in clinical status and cardiac function or in those who successfully restrict dietary sodium intake. These patients may undergo cautious weaning of diuretic dose and frequency with careful observation for recurrent fluid retention. · Patients and caregivers should be given education on the early signs of fluid retention and the plan for initial therapy. · Selected patients may be educated to adjust daily dose of diuretic in response to weight gain from fluid overload. <u>Evaluation and management of patients with acute decompensated heart failure</u> · Patients admitted with acute decompensated heart failure and evidence of fluid overload be treated initially with loop diuretics; usually given intravenously rather than orally. Ultrafiltration may be considered in lieu of diuretics. · Diuretics should be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion, without inducing an excessively rapid reduction in intravascular volume or serum electrolytes. · Monitoring of daily weights, intake and output is recommended to assess clinical efficacy of diuretic therapy. · Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension and gout is recommended in patients treated with diuretics, especially when high doses or combination therapy is used. · Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis.

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	· When congestion fails to improve in response to diuretic therapy, the following options should be considered: o Re-evaluating the presence/absence of congestion. o Sodium and fluid restriction. o Increasing doses of loop diuretic. o Continuous infusion of a loop diuretic. o Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide). o Ultrafiltration may be considered as well.
European Society of Cardiology: **European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure (2012)**[39]	Treatments recommended in potentially all patient with symptomatic (New York Heart Association [NYHA] functional class II-IV) systolic heart failure · ACE inhibitors are recommended, in addition to a β-blocker, for all patients with an ejection fraction ≤40% to reduce the risk of hospitalization and the risk of premature death. · A β-blocker is recommended, in addition to an ACE inhibitor (or ARB if ACE inhibitor is not tolerated), for all patients with an ejection fraction ≤40% to reduce the risk of heart failure hospitalization and the risk of premature death. Recommendations for controlling the ventricular rate in patients with symptomatic heart failure (NYHA functional class II-IV), left ventricular systolic dysfunction, persistent/permanent atrial fibrillation and no evidence of acute decompensation · Step 1: a β-blocker is recommended as the preferred first line treatment to control the ventricular rate because of the associated benefits of this treatment (i.e., reducing the risk of hospitalization for worsening heart failure, reducing the risk of premature death). · Step 2: digoxin is recommended as the preferred second drug, in addition to a β-blocker, to control the ventricular rate in patients with an inadequate response to a β-blocker. Recommendations for the management of ventricular arrhythmias in heart failure · It is recommended that treatment with an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist should be optimized in patients with ventricular arrhythmias. Recommendations for the pharmacological treatment of stable angina pectoris in patients with symptomatic heart failure (NYHA functional class II-IV) and left ventricular systolic dysfunction · Step 1: a β-blocker is recommended as the preferred first line treatment to relieve angina because of the associated benefits of this treatment (i.e., reducing the risk of heart failure hospitalization, risk of premature death). o Amlodipine should be considered as a potential alternative to a β-blocker in patients unable to tolerate a β-blocker, to relieve angina. · Step 2: add a second anti-anginal drug to a β-blocker. o The addition of amlodipine is recommended when angina persists despite treatment with a β-blocker (or alternative agent), to relive angina. · Step 3: Coronary revascularization is recommended when angina persists despite treatment with two antianginal drugs. o Diltiazem or verapamil are not recommended because of their negative

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	inotropic action and risk of worsening heart failure. <u>Recommendations for the treatment of hypertension in patients with symptomatic heart failure (NYHA functional class II-IV) and left ventricular systolic dysfunction</u> · Step 1: one or more of an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist is recommended as first, second, and third line therapy, respectively, because of their associated benefits (i.e., reducing the risk of heart failure hospitalization, reducing the risk of premature death). · Step 2: a thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, and mineralocorticoid receptor antagonist. · Step 3: o Amlodipine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic. o Hydralazine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic. o Felodipine should be considered when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), β-blocker, mineralocorticoid receptor antagonist, and diuretic. <u>Treatment of acute heart failure</u> · A β-blocker is recommended in patients with an ejection fraction ≤40%, after stabilization, to reduce the risk of death and recurrent MI.
American Heart Association/ American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation (2014)**[40]	<u>Recommendations for risk-based antithrombotic therapy</u>: Class I · In patients with atrial fibrillation (AF), antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences (Level of Evidence: C). · Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent (Level of Evidence: B). · In patients with nonvalvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk (Level of Evidence: B). · For patients with AF who have mechanical heart valves, warfarin is recommended and the target international normalized ratio (INR) should be based on type and location of the prosthesis (Level of Evidence: B). · For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran, rivaroxaban, or apixaban (Level of Evidence: B). · For patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable (Level of Evidence: A) · For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended

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	(Level of Evidence: C). · Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks (Level of Evidence: C). · Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding (Level of Evidence: C). · For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated (Level of Evidence: C). · Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually (Level of Evidence: B). · For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF (Level of Evidence: C). Class IIa · For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 0, it is reasonable to omit antithrombotic therapy (Level of Evidence: B). · For patients with nonvalvular AF with a CHA_2DS_2-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation (Level of Evidence: B). Class IIb · For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Level of Evidence: C). · For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a CHA_2DS_2-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established (Level of Evidence: C). · In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture (Level of Evidence: C). · Following coronary revascularization (percutaneous or surgical) in patients with AF and a CHA_2DS_2-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B). Class III: No Benefit · The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits (Level of Evidence: C). Class III: Harm · The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve (Level of Evidence: B).

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	Recommendations for rate control: Class I · Control of the ventricular rate using a beta blocker or nondihydropyridine (non-DHP) calcium channel blocker (CCB) is recommended for patients with paroxysmal, persistent, or permanent AF (Level of Evidence: B). · Intravenous administration of a beta blocker or non-DHP CCB is recommended to slow the ventricular heart rate in the acute setting in patients without pre-excitation. In hemodynamically unstable patients, electrical cardioversion is indicated (Level of Evidence: B). · In patients who experience AF-related symptoms during activity, the adequacy of heart rate control should be assessed during exertion, adjusting pharmacological treatment as necessary to keep the ventricular rate within the physiological range (Level of Evidence: C). Class IIa · A heart rate control (resting heart rate <80 beats per minute [bpm]) strategy is reasonable for symptomatic management of AF (Level of Evidence: B). · Intravenous amiodarone can be useful for rate control in critically ill patients without pre-excitation (Level of Evidence: B). · Atrioventricular (AV) nodal ablation with permanent ventricular pacing is reasonable to control heart rate when pharmacological therapy is inadequate and rhythm control is not achievable (Level of Evidence: B). Class IIb · A lenient rate-control strategy (resting heart rate <110 bpm) may be reasonable as long as patients remain asymptomatic and left ventricular systolic function is preserved (Level of Evidence: B). · Oral amiodarone may be useful for ventricular rate control when other measures are unsuccessful or contraindicated (Level of Evidence: C). Class III: Harm · AV nodal ablation with permanent ventricular pacing should not be performed to improve rate control without prior attempts to achieve rate control with medications (Level of Evidence: C). · Non-DHP CCBs should not be used in patients with decompensated HF as these may lead to further hemodynamic compromise (Level of Evidence: C). · In patients with pre-excitation and AF, digoxin, non-DHP CCBs, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in ventricular fibrillation. (Level of Evidence: B). · Dronedarone should not be used to control the ventricular rate in patients with permanent AF as it increases the risk of the combined endpoint of stroke, myocardial infarction, systemic embolism, or cardiovascular death (Level of Evidence: B). Recommendations for Thromboembolism Prevention: Class I · For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the CHA_2DS_2-VASc score and the method used to restore sinus rhythm (Level of Evidence: B). · For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at

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	least four weeks after cardioversion unless contraindicated (Level of Evidence: C). · For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy (Level of Evidence: C). · Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile (Level of Evidence: C). Class IIa · For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks (Level of Evidence: B). · For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion (Level of Evidence: C). Class IIb · For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation (Level of Evidence: C). <u>Recommendations for pharmacological cardioversion</u> Class I · Flecainide, dofetilide, propafenone, and intravenous ibutilide are useful for pharmacological cardioversion of AF or atrial flutter, provided contraindications to the selected drug are absent (Level of Evidence: A). Class IIa · Administration of oral amiodarone is a reasonable option for pharmacological cardioversion of AF (Level of Evidence: A). · Propafenone or flecainide (“pill-in-the-pocket”) in addition to a beta blocker or non-DHP CCB is reasonable to terminate AF outside the hospital once this treatment has been observed to be safe in a monitored setting for selected patients (Level of Evidence: B). Class III: Harm · Dofetilide therapy should not be initiated out of hospital because of the risk of excessive QT prolongation that can cause torsades de pointes (Level of Evidence: B). <u>Recommendations for antiarrhythmic drugs to maintain sinus rhythm</u> Class I · Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended (Level of Evidence: C). · The following antiarrhythmic drugs are recommended in patients with AF to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Level of Evidence: A):

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	o Amiodarone o Dofetilide o Dronedarone o Flecainide o Propafenone o Sotalol · The risks of the antiarrhythmic drug, including proarrhythmia, should be considered before initiating therapy with each drug (Level of Evidence: C). · Because of its potential toxicities, amiodarone should only be used after consideration of risks and when other agents have failed or are contraindicated (Level of Evidence: C). Class IIa · A rhythm-control strategy with pharmacological therapy can be useful in patients with AF for the treatment of tachycardia-induced cardiomyopathy (Level of Evidence: C). Class IIb · It may be reasonable to continue current antiarrhythmic drug therapy in the setting of infrequent, well-tolerated recurrences of AF when the drug has reduced the frequency or symptoms of AF (Level of Evidence: C). Class III: Harm · Antiarrhythmic drugs for rhythm control should not be continued when AF becomes permanent (Level of Evidence: C), including dronedarone (Level of Evidence: B). · Dronedarone should not be used for treatment of AF in patients with New York Heart Association class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks. (Level of Evidence: B). <u>Upstream therapy</u> Class IIa · An angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is reasonable for primary prevention of new-onset AF in patients with HF with reduced left ventricular ejection fraction (Level of Evidence: B). Class IIb · Therapy with an ACE inhibitor or ARB may be considered for primary prevention of new-onset AF in the setting of hypertension (Level of Evidence: B). · Statin therapy may be reasonable for primary prevention of new-onset AF after coronary artery surgery (Level of Evidence: A). Class III: No Benefit · Therapy with an ACE inhibitor, ARB, or statin is not beneficial for primary prevention of AF in patients without cardiovascular disease (Level of Evidence: B).
National Institute for Health and Clinical Excellence: **Atrial Fibrillation: The Management of Atrial Fibrillation (2014)**[41]	<u>Interventions to prevent stroke</u> · Do not offer stroke prevention to people aged <65 years with atrial fibrillation (AF) and no risk factors other than their sex (that is, very low risk of stroke equating to CHA_2DS_2-VASc score of 0 for men or 1 for women). · Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. Take the bleeding risk into account. · Offer anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account. · Discuss the options for anticoagulation with the person and base the choice

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	on their clinical features and preferences. · Apixaban o Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorization, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as: § Prior stroke of transient ischemic attack (TIA). § Age 75 years or older. § Hypertension. § Diabetes mellitus. § Symptomatic heart failure. · Dabigatran etexilate o Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors: § Previous stroke, TIA, or systemic embolism. § Left ventricular ejection fraction (LVEF) <40%. § Symptomatic heart failure (HF) of New York Heart Association (NYHA) class 2 or above. § Age 75 years or older. § Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease, or hypertension. · Rivaroxaban o Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular AF with one or more risk factors such as: § Congestive heart failure. § Hypertension. § Age 75 years or older. § Diabetes mellitus. § Prior stroke or TIA. · The decision about whether to start treatment with a new oral anticoagulant should be made after an informed discussion between the clinician and the person about the risks and benefits of the agent compared with the alternatives, including warfarin. For people who are taking warfarin, the potential risks and benefits of switching to a different oral agent should be considered in light of their level of international normalized ratio (INR) control. <u>Assessing anticoagulation control with vitamin K antagonists</u> · Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR: o Use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing. o Exclude measurements taken during the first six weeks of treatment. o Calculate TTR over a maintenance period of at least six months. · Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following: o Two INR values higher than 5 or one INR value higher than 8 within the past six months. o Two INR values less than 1.5 within the past six months. o TTR <65%.

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	· When assessing anticoagulation, take into account and if possible address the following factors that may contribute to poor anticoagulation control: Cognitive function, adherence, illness, drug interactions, and lifestyle factors including diet and alcohol consumption. · If poor anticoagulation control cannot be improved, evaluate the risks and benefits of alternative stroke prevention strategies and discuss these with the person. When to offer rate and rhythm control · Offer rate control as the first-line strategy to people with AF, except in people whose AF has a reversible cause, who have HF thought to be primarily caused by AF, with new-onset AF, with atrial flutter whose condition is considered suitable for an ablation strategy to restore sinus rhythm, and for whom a rhythm control strategy would be more suitable based on clinical judgement. Rate control · Offer either a standard beta-blocker (that is, a beta-blocker other than sotalol) or a rate-limiting calcium channel blocker (CCB) as initial monotherapy to people with AF who need drug treatment as part of a rate control strategy. Base the choice of drug on the person's symptoms, heart rate, comorbidities, and preferences when considering drug treatment. · Consider digoxin monotherapy for people with non-paroxysmal AF only if they are sedentary. · If monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, consider combination therapy with any two of the following: a beta-blocker, diltiazem, and digoxin. · Do not offer amiodarone for long-term rate control. Rhythm control · Consider pharmacological and/or electrical rhythm control for people with AF whose symptoms continue after heart rate has been controlled or for whom a rate-control strategy has not been successful. Drug treatment for long-term rhythm control · Assess the need for drug treatment for long-term rhythm control, taking into account the person's preferences, associated comorbidities, risks of treatment, and likelihood of recurrence of AF. · If drug treatment for long-term rhythm control is needed, consider a standard beta-blocker as first-line treatment unless there are contraindications. · If beta-blockers are contraindicated or unsuccessful, assess the suitability of alternative drugs for rhythm control, taking comorbidities into account. · Dronedarone is recommended as an option for the maintenance of sinus rhythm after successful cardioversion in people with paroxysmal or persistent atrial fibrillation: o Whose AF is not controlled by first-line therapy (usually including beta-blockers), that is, as a second-line treatment option and after alternative options have been considered AND o Who have at least one of the following cardiovascular risk factors: § Hypertension requiring drugs of at least two different classes. § Diabetes mellitus.

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	§ Previous TIA, stroke, or systemic embolism. § Left atrial diameter of 50 mm or greater, OR § Age ≥70 years, AND o Who do not have left ventricular systolic dysfunction, AND o Who do not have a history of, or current, HF. · People who do not meet the criteria above who are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop. · Consider amiodarone for people with left ventricular impairment or HF. · Do not offer class 1c antiarrhythmic drugs such as flecainide or propafenone to people with known ischemic or structural heart disease. · Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (such as alcohol, caffeine), a 'no drug treatment' strategy or a 'pill-in-the-pocket' strategy should be considered and discussed with the person.
American College of Chest Physicians: **Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery (2005)**[42]	· β-blockers and nondihydropyridine calcium channel blockers are recommended as first- and second-line agents to control ventricular response rate in AF after cardiac surgery. Digoxin has shown little efficacy in this patient population. · Current medical evidence does not support the use of digitalis for the prevention of postoperative AF. · No recommendation can be made regarding the use of digoxin for rhythm control of postoperative AF or atrial flutter. · Agents with proarrhythmic properties and those that are contraindicated in patients with coronary artery disease have not been shown to be effective in controlling the ventricular response rate in AF after cardiac surgery. · Amiodarone is the recommended first-line agent for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with depressed left ventricular function who do not need urgent electrical cardioversion. · Sotalol and Class Ia antiarrhythmics are the recommended first-line agents for pharmacologic rhythm control of postoperative AF or atrial flutter in patients with coronary artery disease without CHF. · When prophylaxis to prevent postoperative AF is indicated, β-blockers are the recommended agents. · Sotalol may be an alternative therapy to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option. · Amiodarone may also be considered as an alternative therapy to β-blockers to prevent postoperative AF, but its ability to cause toxicity may not make it a favorable option.
American College of Cardiology/American Heart Association/ European Society of Cardiology Committee for Practice Guidelines: **Guidelines for Management of Patients With Ventricular**	Drug therapy for ventricular arrhythmias · β-blockers are currently the mainstay of pharmacologic therapy for the treatment of arrhythmias, due to their safety profile and effectiveness. · Other than β-blockers, alternative antiarrhythmic agents currently available have not been proven effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of sudden cardiac death. · For patients that are arrhythmia-prone, antiarrhythmic agents may be effective as adjunctive therapy in particular situations. · Caution should be used when any antiarrhythmic agent is used for therapy, as there are many side effects associated with these agents. · β-blockers, or alternatively, amiodarone or sotalol, may be used in patients

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Arrhythmias and the Prevention of Sudden Cardiac Death (2006)[43]	with ventricular tachycardia who do not meet criteria for an implantable cardioverter-defibrillator. · Sotalol or, alternatively the combination of β-blockers and amiodarone, may be used in patients with implantable cardioverter-defibrillators who have recurrent ventricular tachycardia/ventricular fibrillation with frequent appropriate implantable cardioverter-defibrillator firing. Ventricular arrhythmia and sudden cardiac death related to specific pathology Left ventricular dysfunction due to prior MI: · Amiodarone, often in combination with β-blockers, can be useful for patients with left ventricular dysfunction due to prior MI and symptoms due to ventricular tachycardia unresponsive to β-blocking agents. · Sotalol is reasonable therapy to reduce symptoms resulting from ventricular tachycardia for patients with left ventricular dysfunction due to prior MI unresponsive to β-blocking agents. · Alternative therapies to the implantable cardioverter-defibrillator to improve symptoms due to frequent episodes of sustained ventricular tachycardia or ventricular fibrillation in patients with left ventricular dysfunction due to prior MI include agents such as amiodarone or sotalol. · To reduce symptoms in patients due to recurrent hemodynamically stable ventricular tachycardia with left ventricular dysfunction due to prior MI and who cannot or refuse to have an implantable cardioverter-defibrillator implanted, amiodarone may be used as an alternative therapy. · To improve symptoms in patients with left ventricular dysfunction due to prior MI and recurrent hemodynamically stable ventricular tachycardia whose LVEF is >40% and an implantable cardioverter-defibrillator is not appropriate, amiodarone may be considered an alternative treatment option. · In patients with left ventricular dysfunction due to prior MI where an implantable cardioverter-defibrillator is indicated but is not appropriate or desired by the patient, amiodarone may be considered an alternative treatment option. · Prophylactic antiarrhythmic drug therapy is not indicated to reduce mortality in patients with asymptomatic nonsustained ventricular arrhythmias. · Class Ic antiarrhythmic agents are not recommended in patients with a past history of MI. Congenital heart disease: · Prophylactic antiarrhythmic therapy is not indicated for asymptomatic patients with congenital heart disease and isolated premature ventricular contractions. Metabolic and inflammatory conditions: · Antiarrhythmic therapy can be useful in patients with symptomatic non-sustained ventricular tachycardia or sustained ventricular tachycardia during the acute phase of myocarditis. Pericardial disease: · Prophylactic antiarrhythmic therapy generally is not indicated for primary prevention of sudden cardiac death in patients with pulmonary arterial hypertension or other pulmonary conditions.

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	Ventricular arrhythmias associated with cardiomyopathies Dilated cardiomyopathy (nonischemic): · Amiodarone may be considered for sustained ventricular tachycardia or ventricular fibrillation in patients with nonischemic dilated cardiomyopathy. Hypertrophic cardiomyopathy · Amiodarone therapy can be effective for treatment in patients with hypertrophic cardiomyopathy with a history of sustained ventricular tachycardia and/or ventricular fibrillation when implantable cardioverter-defibrillator is not feasible. · Amiodarone may be considered for primary prophylaxis against sudden cardiac death in patients with hypertrophic cardiomyopathy who have one or more major risk factor for sudden cardiac death, if implantable cardioverter-defibrillator implantation is not feasible. Arrhythmogenic right ventricular cardiomyopathy · Amiodarone or sotalol can be effective for treatment of sustained ventricular tachycardia or ventricular fibrillation in patients with arrhythmogenic right ventricular cardiomyopathy when implantable cardioverter-defibrillator implantation is not feasible. Heart failure · Amiodarone, sotalol and/or other β-blockers are recommended pharmacological adjuncts to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in otherwise optimally treated patients with heart failure. · Amiodarone is indicated for the suppression of acute hemodynamically compromising ventricular or supraventricular tachyarrhythmias when cardioversion and/or correction of reversible causes have failed to terminate the arrhythmia or prevent its early recurrence. · Amiodarone, sotalol, and/or β-blockers may be considered as pharmacological alternatives to implantable cardioverter-defibrillator therapy to suppress symptomatic ventricular tachyarrhythmias (both sustained and nonsustained) in optimally treated patients with heart failure for whom implantable cardioverter-defibrillator therapy is not feasible. Genetic arrhythmia syndromes Long QT syndrome: · β-blockers are recommended for patients with a long QT syndrome clinical diagnosis (i.e., in the presence of prolonged QT interval). · Implantation of an implantable cardioverter-defibrillator along with use of β-blockers is recommended for long QT syndrome patients with previous cardiac arrest and who have reasonable expectation of survival with a good functional status for more than one year. · β-blockers can be effective to reduce sudden cardiac death in patients with a molecular long QT syndrome analysis and normal QT interval. · Implantation of an implantable cardioverter-defibrillator with continued use of β-blockers can be effective to reduce sudden cardiac death in long QT syndrome patients experiencing syncope and/or ventricular tachycardia while receiving β-blockers and who have reasonable expectation of survival with a

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	good functional status for more than one year. Short QT syndrome and Brugada syndrome: · Quinidine might be reasonable for the treatment of electrical storm in patients with Brugada syndrome. Catecholaminergic polymorphic ventricular tachycardia: · β-blockers are indicated for patients who are clinically diagnosed with catecholaminergic polymorphic ventricular tachycardia on the basis of the presence of spontaneous or documented stress-induced ventricular arrhythmias. · β-blockers can be effective in patients without clinical manifestations when the diagnosis of catecholaminergic polymorphic ventricular tachycardia is established during childhood based on genetic analysis. · β-blockers may be considered for patients with catecholaminergic polymorphic ventricular tachycardia who were genetically diagnosed in adulthood and never manifested clinical symptoms of tachyarrhythmias. Arrhythmias in structurally normal hearts Idiopathic ventricular tachycardia: · Drug therapy with β-blockers and/or calcium channel blockers can be useful in patients with structurally normal hearts with symptomatic ventricular tachycardia arising from the right ventricle. Ventricular arrhythmias and sudden cardiac death related to specific populations Pregnancy: · In pregnant women with the long QT syndrome who have had symptoms, it is beneficial to continue β-blocker medications throughout pregnancy and afterward, unless there are definite contraindications. Elderly: · The dosing and titration schedule of antiarrhythmic drugs prescribed to elderly patients should be adjusted to the altered pharmacokinetics of such patients.
European Society of Cardiology: **Guidelines on diagnosis and management of hypertrophic cardiomyopathy (2014)**[44]	· Patients with symptomatic left ventricular outflow tract obstruction should be treated initially with non-vasodilating β-blockers titrated to maximum tolerable dose. · If β-blockers alone are ineffective, disopyramide titrated to a maximum tolerated dose (usually 400 to 600 mg/day) may be added. · Verapamil can be used when β-blockers are contraindicated or ineffective, but close monitoring is required in patients with severe obstruction (≥100 mmHg) or elevated pulmonary artery systolic pressures, as it can provoke pulmonary edema. · Nifedipine and other dihydropyridine calcium antagonists are not recommended. · Low-dose loop or thiazide diuretics may be used cautiously to improve dyspnea, but it is important to avoid hypovolemia. · In patients without left ventricular outflow tract obstruction, An ACE inhibitor (or ARB if ACE inhibitor not tolerated) should be considered, in addition to a ß-blocker, for patients who have an LVEF <50%, to reduce the risks of HF

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	hospitalization and premature death.
Eighth Joint National Committee (JNC 8): **2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults (2014)**[45]	· Pharmacologic treatment should be initiated in patients ≥60 years of age to lower blood pressure at systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <150 mm Hg and goal diastolic blood pressure <90 mm Hg. Adjustment of treatment is not necessary if treatment results in lower blood pressure and treatment is well tolerated and without adverse effects on health or quality of life. · In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at diastolic blood pressure ≥90 mm Hg to a goal diastolic blood pressure <90 mm Hg. · In patients <60 years of age, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥150 mm Hg to a goal diastolic blood pressure <140 mm Hg. · For patients ≥18 years of age with chronic kidney disease or diabetes, pharmacologic treatment should be initiated to lower blood pressure at systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg and to a goal systolic blood pressure <140 mm Hg and goal diastolic blood pressure <90 mm Hg. · Initial antihypertensive treatment for the general nonblack population, including those with diabetes, should include thiazide-type diuretic, calcium channel blocker (CCB), ACE inhibitor, or ARB. · Initial antihypertensive treatment for the general black population, including those with diabetes, should include thiazide-type diuretic or CCB. · For patients ≥18 years of age with chronic kidney disease regardless of race or diabetes status, initial (or add-on) treatment should include an ACE inhibitor or ARB to improve kidney outcomes. · The main goal of antihypertensive treatment is to attain and maintain goal blood pressure. · If goal blood pressure is not attained within a month of treatment, the dose of the initial drug should be increased or second drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. · If goal is not achieved with two drugs, a third drug from the thiazide-type diuretic, CCB, ACE inhibitor, or ARB classes should be added. · An ACE inhibitor and ARB should not be used together. · Antihypertensive classes can be used if the patient is unable to achieve goal blood pressure with three agents or had a contraindication to a preferred class. · If blood pressure is not able to be achieved or in complicated patients, referral to a hypertension specialist may be indicated.
World Health Organization/ International Society of Hypertension: **2003 World Health Organization/ International Society of Hypertension Statement on Management of Hypertension (2003)**[46]	· When used as monotherapy, a diuretic or a calcium channel blocker may be more effective than an ACE inhibitor or a β-blocker in African American patients and older patients. · Compelling indications for the use of a medication from a specific drug class include elderly patients with isolated systolic hypertension (diuretics and dihydropyridine calcium channel blockers), renal disease (ACE inhibitors and ARBs), post-MI (ACE inhibitors and β-blockers), left ventricular dysfunction (ACE inhibitors), congestive heart failure (β-blockers, ACE inhibitors and diuretics), left ventricular hypertrophy (ARBs) and cerebrovascular disease (diuretics and ACE inhibitors).

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European Society of Hypertension/European Society of Cardiology: **2007 Guidelines for the Management of Hypertension (2007)[47], Reappraisal of Guidelines on Hypertension Management (2009)[48]**	· In order to optimize treatment initiation, intensity and goals, it is important to assess total cardiovascular risk in patients with hypertension which must include a search for subclinical organ damage. · In general, early introduction of blood pressure lowering treatments, before organ damage develops or becomes irreversible or before cardiovascular events occur, is recommended. · There is evidence that certain drug classes may be preferred in specific patient populations: left ventricular hypertrophy (ACE inhibitors, ARBs and calcium channel blockers), asymptomatic atherosclerosis (calcium channel blockers and ACE inhibitors), microalbuminuria and renal dysfunction (ACE inhibitors and ARBs), previous stroke (any antihypertensive), previous MI (ACE inhibitors, β-blockers and ARBs), angina (calcium channel blockers and β-blockers), heart failure (diuretics, ACE inhibitors, β-blockers, ARBs and aldosterone antagonists), recurrent atrial fibrillation (ACE inhibitors and ARBs), permanent atrial fibrillation (β-blockers and nondihydropyridine calcium channel blockers), end stage renal disease/proteinuria (ACE inhibitors, ARBs and loop diuretics), metabolic syndrome (ACE inhibitors, ARBs and calcium channel blockers), diabetes (ACE inhibitors and ARBs), pregnancy (methyldopa, calcium channel blockers and β-blockers) and African American patients (calcium channel blockers and diuretics). · Available evidence justifies the use of aliskiren in hypertension, particularly in combination with other agents. · Many patients will require more than one medication to control blood pressure. Patients may be started on monotherapy or combination therapy. Initial combination therapy should be considered in patients with grade II or III hypertension or patients with high or very high cardiovascular risk. · Fixed combination medications can favor compliance and simplify regimens. · When combining different classes of antihypertensive medications, consider medications which have different and complementary mechanisms of action, and that there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and the combination is likely to be well tolerated. · Combinations that can be recommended for priority use based on trial evidence of outcome reduction include a diuretic with an ACE inhibitor, ARB or calcium channel blocker and an ACE inhibitor with a calcium channel blocker. · Avoid β-blocker/diuretic combination unless required for other reasons. · If triple therapy is needed, the most rational combination is a blocker of the rennin-angiotensin system, a calcium channel blocker and a diuretic at effective doses. · A β- or α-blocker may be included in a triple therapy approach depending on clinical circumstances. · Antihypertensive treatment is highly beneficial in elderly patients and treatment may be initiated with a thiazide diuretic, ACE inhibitor, calcium channel blocker, ARB or β-blocker. · Blood pressure lowering drugs should be continued or initiated in patients 80 years of age, starting with monotherapy and adding a second drug, if needed. The decision to treat should be made on an individual basis and patients should be carefully monitored. · Calcium channel blockers, ARBs and thiazide diuretics have been shown to be effective in treating isolated systolic hypertension. · Antihypertensive treatment should always be initiated in diabetic patients

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	when blood pressure is 140/90 mm Hg or higher; however, there is evidence in favor of initiating treatment with high normal blood pressure. · The blood pressure goal of <130/80 mm Hg is not supported by outcome evidence from trials and is difficult for the majority of patients to achieve; therefore, its realistic to recommend only to pursue a sizeable blood pressure reduction without indicating a goal that is unproven. · In hypertensive diabetic patients, tight blood glucose control (glycosylated hemoglobin to 6.5%) is beneficial, particularly in combination with effective blood pressure control, on improving microvascular complications. Tight glucose control should not be pursued abruptly and patients should be monitored closely due to the increased risk of severe hypoglycemic episodes.
European Society of Hypertension/European Society of Cardiology: **2013 Guidelines for the management of arterial hypertension (2013)**[49]	The 2013 guidelines on hypertension of the European Society of Hypertension and the European Society of Cardiology follow the guidelines jointly issued by the two societies in 2003 and 2007. <u>Treatment strategies and choice of antihypertensive drugs</u> · Diuretics (including thiazides, chlorthalidone, and indapamide), beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations. · Some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of organ damage. · Initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline blood pressure (BP) or at high cardiovascular (CV) risk. · The combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged. · Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable. · Combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favored, because reducing the number of daily pills improves adherence, which is low in patients with hypertension. <u>Treatment strategies in white-coat and masked hypertension</u> · In white-coat hypertensives without additional risk factors, therapeutic intervention may be limited to lifestyle changes only, but this decision should be accompanied by close follow-up. · In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic organ damage, drug treatment may be considered in addition to lifestyle changes. · In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension. <u>Antihypertensive treatment strategies in the elderly</u> · In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg. · In fit elderly patients <80 years old antihypertensive treatment may be

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	considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated. · In individuals older than 80 years with an initial SBP ≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions. · In frail elderly patients, it is recommended to leave decisions on antihypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment. · Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes an octogenarian. · All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension. Treatment strategies in hypertensive women · Hormone therapy and selective estrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD. · If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks. · Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended. · Drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical organ damage or symptoms. · In women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal hemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered. · In women with child-bearing potential RAS blockers are not recommended and should be avoided. · Methyldopa, labetalol, and nifedipine should be considered preferential antihypertensive drugs in pregnancy. Intravenous labetalol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia). Treatment strategies in patients with diabetes · While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg. · A SBP goal <140 mmHg is recommended in patients with diabetes. · The DBP target in patients with diabetes is recommended to be <85 mmHg. · All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. · It is recommended that individual drug choice takes comorbidities into account. · Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes Treatment strategies in hypertensive patients with metabolic syndrome · Lifestyle changes, particularly weight loss and physical exercise, are to be

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	recommended to all individuals with the metabolic syndrome. These interventions improve not only BP, but the metabolic components of the syndrome and delay diabetes onset. · As the metabolic syndrome can be considered a 'pre-diabetic' state, antihypertensive agents potentially improving or at least not worsening insulin sensitivity, such as RAS blockers and calcium antagonists, should be considered as the preferred drugs. Beta-blockers (with the exception of vasodilating beta-blockers) and diuretics should be considered only as additional drugs, preferably in association with a potassium-sparing agent. · It is recommended to prescribe antihypertensive drugs with particular care in hypertensive patients with metabolic disturbances when BP is ≥140/90 mmHg after a suitable period of lifestyle changes, and to maintain BP <140/90 mmHg. · BP lowering drugs are not recommended in individuals with metabolic syndrome and high normal BP. <u>Therapeutic strategies in hypertensive patients with nephropathy</u> · Lowering SBP to <140 mmHg should be considered. · When overt proteinuria is present, SBP values <130 mmHg may be considered, provided that changes in eGFR are monitored. · RAS blockers are more effective in reducing albuminuria than other antihypertensive agents, and are indicated in hypertensive patients in the presence of microalbuminuria or overt proteinuria. · Reaching BP goals usually requires combination therapy, and it is recommended to combine RAS blockers with other antihypertensive agents. · Combination of two RAS blockers, though potentially more effective in reducing proteinuria, is not recommended. · Aldosterone antagonists cannot be recommended in chronic kidney disease (CKD), especially in combination with a RAS blocker, because of the risk of excessive reduction in renal function and of hyperkalemia. <u>Therapeutic strategies in hypertensive patients with cerebrovascular disease</u> · It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke irrespective of BP level, although clinical judgement should be used in the face of very high SBP values. · Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or transient ischemic attack (TIA), even when initial SBP is in the 140 to 159 mmHg range. · In hypertensive patients with a history of stroke or TIA, a SBP goal of <140 mmHg should be considered. · In elderly hypertensives with previous stroke or TIA, SBP values for intervention and goal may be considered to be somewhat higher. · All drug regimens are recommended for stroke prevention, provided that BP is effectively reduced. <u>Therapeutic strategies in hypertensive patients with heart disease</u> · In hypertensive patients with CHD, a SBP goal <140 mmHg should be considered. · In hypertensive patients with a recent myocardial infarction, beta-blockers are recommended. In case of other CHD all antihypertensive agents can be used, but beta-blockers and calcium antagonists are to be preferred for symptomatic reasons (angina).

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	· Diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers, and/or mineralocorticoid receptor antagonists are recommended in patients with heart failure or severe left ventricular (LV) dysfunction to reduce mortality and hospitalization. · In patients with heart failure and preserved ejection fraction (EF), there is no evidence that antihypertensive therapy per se or any particular drug is beneficial. However, in these patients, as well as in patients with hypertension and systolic dysfunction, lowering SBP to around 140 mmHg should be considered. Treatment guided by relief of symptoms (congestion with diuretics, high heart rate with beta-blockers, etc.) should also be considered. · ACE inhibitors and angiotensin receptor blockers (and beta-blockers and mineralocorticoid receptor antagonists if heart failure coexists) should be considered as antihypertensive agents in patients at risk of new or recurrent atrial fibrillation. · It is recommended that all patients with left ventricular hypertrophy (LVH) receive antihypertensive agents. · In patients with LVH, initiation of treatment with one of the agents that have shown a greater ability to regress LVH should be considered, i.e. ACE inhibitors, angiotensin receptor blockers, and calcium antagonists. <u>Therapeutic strategies in hypertensive patients with atherosclerosis, arteriosclerosis, and peripheral artery disease (PAD)</u> · In the presence of carotid atherosclerosis, prescription of calcium antagonists and ACE inhibitors should be considered as these agents have shown a greater efficacy in delaying atherosclerosis progression than diuretics and beta-blockers. · In hypertensive patients with a pulse wave velocity above 10 m/s, all antihypertensive drugs should be considered provided that a BP reduction to <140/90 mmHg is consistently achieved. · Antihypertensive therapy is recommended in hypertensive patients with PAD to achieve a goal of <140/90 mmHg, because of their high risk of myocardial infarction, stroke, heart failure, and CV death. · Though a careful follow up is necessary, beta-blockers may be considered for the treatment of arterial hypertension in patients with PAD, since their use does not appear to be associated with exacerbation of PAD symptoms.
National Institute for Health and Clinical Excellence: **Hypertension: The Clinical Management of Primary Hypertension in Adults (2011)**[50] **Reviewed Oct 2013**	· Patients <55 years should be offered a step 1 antihypertensive with an ACE inhibitor or ARB. If an ACE inhibitor is not tolerated, offer an ARB. · Do not combine an ACE inhibitor with an ARB for the treatment of hypertension. · Offer a step 1 antihypertensive (ACE inhibitor, ARB) with a calcium channel blocker to patients >55 years of age and to black patients of African or Caribbean origin of any age. If a calcium channel blocker is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. · For patients who are already receiving treatment with bendroflumethiazide or hydrochlorothiazide and who are stable and well controlled, continue treatment as is. · β-blockers are not a preferred initial therapy for hypertension; however, β-blockers may be considered in younger patients, particularly: o Patients with an intolerance or contraindication to ACE inhibitors and ARBs.

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	o Women of child-bearing potential. o People with evidence of increased sympathetic drive. · If treatment is initiated with a β-blocker and a second antihypertensive is required, add a calcium channel blocker over a thiazide-like diuretic to reduce the risk of developing diabetes. · If blood pressure is not controlled with a step 1 antihypertensive, offer a step 2 antihypertensive with a calcium channel blocker in combination with an ACE inhibitor or an ARB. If a calcium channel blocker is not appropriate or if there is evidence of heart failure or a high risk of heart failure, offer a thiazide-like diuretic. · For black patients of African or Caribbean origin, consider an ARB over an ACE inhibitor, in combination with a calcium channel blocker. · If three drugs are required to control blood pressure, the combination of an ACE inhibitor or ARB, calcium channel blocker, and a thiazide-like diuretic should be utilized. · Resistant hypertension should be considered with clinic blood pressure remains >140/90 mm Hg after treatment with the optimal or best tolerated doses of an ACE inhibitor or an ARB plus a calcium channel blocker plus a diuretic. · For treatment of resistant hypertension at step 4: o Consider further diuretic therapy with low-dose spironolactone. o Consider higher-dose thiazide-like diuretic treatment. o If further diuretic therapy for resistant hypertension at step 4 is not tolerated or is contraindicated or ineffective, consider an α-blocker or β-blocker.
International Society on Hypertension in Blacks: **Management of High Blood Pressure in Blacks (2010)**[51]	· To attain and maintain blood pressure (BP) below target levels, multiple antihypertensive drugs will be required in most hypertensive blacks. · Use of two-drug combination therapy when SBP is >15 mm Hg and/or DBP is >10 mm Hg above goal levels is increasingly recommended as first-line therapy. · Two-drug regimens have generally contained a thiazide-type diuretic; however, the combination of a calcium channel blocker (CCB) with either an ACE inhibitor or an ARB has been shown equally efficacious in BP lowering but with demonstrated superiority (CCB+ACE) for hard clinical outcomes compared with the same ACE inhibitor plus a thiazide-type diuretic. · In secondary prevention patients, the combination therapy should include a drug(s) with the appropriate compelling indications. · Certain classes of antihypertensive medications, specifically diuretics and CCBs, lower BP on average more than β-blockers and renin-angiotensin system (RAS) blockers in black patients when used as monotherapies. · In the absence of compelling indications, when BP is near goal levels, monotherapy with a diuretic or a CCB is preferred. · Lifestyle modifications should be initiated in all patients with hypertension, whether or not pharmacotherapy is planned. · ACE inhibitors or ARBs are recommended as alternative monotherapy options in the treatment of hypertension in blacks. The rationale for their lower tier monotherapy recommendation is because they have consistently achieved lesser average reductions in BP relative to that observed with monotherapy using either a diuretic or CCB.
National Kidney Foundation, Kidney Disease Outcomes	· All antihypertensives can be used to lower blood pressure in chronic kidney disease. · Combination therapy is likely to be necessary to achieve blood pressure

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Quality Initiative: **Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease (2004)**[52]	goals. If combination therapy is required, separate prescriptions or fixed-dose combinations may be used as initial therapy. · Antihypertensive regimens should be simplified as much as possible and long-acting agents should be used when possible. · Diuretics should be a component of the antihypertensive regimen in most patients. Other agents should be chosen based on cardiovascular risk profile and compelling indications as follows: heart failure with systolic dysfunction (diuretics, ACE inhibitors, ARBs, β-blockers, calcium channel blockers, aldosterone antagonists), post-MI with systolic dysfunction (ACE inhibitors, ARBs, β-blockers, aldosterone antagonists), post-MI (β-blockers), chronic stable angina (calcium channel blockers, β-blockers), high CAD risk (diuretics, ACE inhibitors, ARBs, β-blockers, calcium channel blockers), recurrent stroke prevention (diuretics, ACE inhibitors, ARBs), and supraventricular tachycardia (β-blockers, nondihydropyridine calcium channel blockers). · Patients with diabetic kidney disease with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or calcium channel blocker. · Patients with nondiabetic kidney disease and spot urine total protein to creatinine ratio of ≥200 mg/g with or without hypertension should be treated with an ACE inhibitor or ARB. If additional medication is needed, diuretics are preferred, followed by a β-blocker or calcium channel blocker. · Kidney transplant patients with chronic kidney disease may be treated with calcium channel blockers, diuretics, ACE inhibitors, ARBs, or β-blockers to reach blood pressure goals.
Kidney Disease Improving Clinical Outcomes Group: **KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (2012)**[53]	Blood pressure management in chronic kidney disease (CKD) non-dialysis (ND) patients without diabetes mellitus · The Work Group recommends that non-diabetic adults with CKD ND and urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. · The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. · The Work Group suggests that non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with blood pressure -lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤ 80 mm Hg diastolic. · The Work Group suggests that an angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) be used in non-diabetic adults with CKD ND and urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated. · The Work Group recommends that an ARB or ACE-I be used in non-diabetic adults with CKD ND and urine albumin excretion >300 mg per 24 hours (or equivalent*) in whom treatment with blood pressure -lowering drugs is indicated.

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	Blood pressure management in CKD ND patients with diabetes mellitus · The Work Group recommends that adults with diabetes and CKD ND with urine albumin excretion <30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >140 mm Hg systolic or >90 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤140 mm Hg systolic and ≤90 mm Hg diastolic. · The Work Group suggests that adults with diabetes and CKD ND with urine albumin excretion >30 mg per 24 hours (or equivalent*) whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated with BP-lowering drugs to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic. · The Work Group suggests that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion of 30 to 300 mg per 24 hours (or equivalent*). · The Work Group recommends that an ARB or ACE-I be used in adults with diabetes and CKD ND with urine albumin excretion >300 mg per 24 hours (or equivalent*). Blood pressure management in kidney transplant recipients (non–dialysis-dependent CKD of any stage with a kidney transplant [CKD T]) · The Work Group suggests that adult kidney transplant recipients whose office blood pressure is consistently >130 mm Hg systolic or >80 mm Hg diastolic be treated to maintain a blood pressure that is consistently ≤130 mm Hg systolic and ≤80 mm Hg diastolic, irrespective of the level of urine albumin excretion. · In adult kidney transplant recipients, choose a blood pressure -lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co morbid conditions. Blood pressure management in children with CKD ND · The Work Group recommends that in children with CKD ND, blood pressure -lowering treatment is started when blood pressure is consistently above the 90th percentile for age, sex, and height. · The Work Group suggests that in children with CKD ND (particularly those with proteinuria), blood pressure is lowered to consistently achieve systolic and diastolic readings less than or equal to the 50th percentile for age, sex, and height, unless achieving these targets is limited by signs or symptoms of hypotension. · The Work Group suggests that an ARB or ACE-I be used in children with CKD ND in whom treatment with blood pressure -lowering drugs is indicated, irrespective of the level of proteinuria. Blood pressure management in elderly persons with CKD ND · Tailor blood pressure treatment regimens in elderly patients with CKD ND by carefully considering age, co-morbidities and other therapies, with gradual escalation of treatment and close attention to adverse events related to blood pressure treatment, including electrolyte disorders, acute deterioration in kidney function, orthostatic hypotension and drug side effects. *Approximate equivalents for albumin excretion rate per 24 hours is expressed as

Clinical Guideline	Recommendations
	protein excretion rate per 24 hours, albumin/creatinine ratio, protein/creatinine ratio, and protein reagent strip results.
American Diabetes Association: **Standards of Medical Care in Diabetes (2015)**[54]	Hypertension/blood pressure control · Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. · People with diabetes and hypertension should be treated to a systolic blood pressure (SBP) goal of <140 mmHg. Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. · Individuals with diabetes should be treated to a diastolic blood pressure (DBP) <90 mmHg. Lower diastolic targets, such as <80 mmHg, may be appropriate for certain individuals, such as younger patients, if they can be achieved without undue treatment burden. · Patients with blood pressure >120/80 mmHg should be advised on lifestyle changes to reduce blood pressure. · Patients with confirmed office-based blood pressure >140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve blood pressure goals. · Lifestyle therapy for elevated blood pressure consists of weight loss, if overweight or obese; a Dietary Approaches to Stop Hypertension (DASH)-style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. · Pharmacological therapy for patients with diabetes and hypertension should comprise a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. · Multiple-drug therapy (including a thiazide diuretic and ACE inhibitor/ARB, at maximal doses) is generally required to achieve blood pressure targets. · If ACE inhibitors, ARBs, or diuretics are used, serum creatinine/estimated glomerular filtration rate and serum potassium levels should be monitored. · In pregnant patients with diabetes and chronic hypertension, blood pressure targets of 110 to 129/65 to 79 mmHg are suggested in the interest of optimizing long-term maternal health and minimizing impaired fetal growth. ACE inhibitors and ARBs are contraindicated during pregnancy. Nephropathy · Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease. · An ACE inhibitor or ARB is not recommended for the primary prevention of diabetic kidney disease in patients with diabetes who have normal blood pressure and normal urine albumin-to-creatinine ratio (UACR) (<30 mg/g). · Either an ACE inhibitor or ARB is suggested for the treatment of the nonpregnant patient with modestly elevated urinary albumin excretion (30 to 299 mg/day) C and is recommended for those with urinary albumin excretion >300 mg/day. · When ACE inhibitors, ARBs, or diuretics are used, monitor serum creatinine and potassium levels for the development of increased creatinine or changes in potassium.
American Academy of Family	General treatment principles · Because relatively few trials have directly compared the different medication

Clinical Guideline	Recommendations
Physicians: **Treatment of Acute Migraine Headache (2011)**[54]	classes available to treat acute migraine, definitive treatment algorithms cannot be developed. · Nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeine-containing combination analgesics may be first-line treatment for mild to moderate migraine, or severe migraine that has previously responded to these agents. · Triptans are considered first-line abortive treatment of moderate to severe migraine, or mild attacks that have not responded to nonprescription medicines. Ergotamine-containing compounds may also be reasonable in this situation.
American Academy of Family Physicians: **Medications for Migraine Prophylaxis (2006)**[56]	· First-line therapies for migraine prophylaxis in adults include propranolol, timolol, amitriptyline, divalproex, sodium valproate, and topiramate. · Second-line therapies for migraine prophylaxis in adults (listed by evidence of effectiveness) include gabapentin, naproxen, naproxen sodium, timed-release dihydroergotamine mesylate, candesartan, lisinopril, atenolol, metoprolol, nadolol, fluoxetine, verapamil, magnesium, vitamin B2, coenzyme Q10, hormone therapy, feverfew, and botulinum toxin type A injections.
American Academy of Neurology/ American Headache Society: **Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults (2012)**[57]	· The following medications are established as effective and should be offered for migraine prevention: o Antiepileptic drugs (AEDs): divalproex sodium, sodium valproate, topiramate o β-Blockers: metoprolol, propranolol, timolol o Triptans: frovatriptan for short-term menstrually associated migraine prevention · The following medications are probably effective and should be considered for migraine prevention: o Antidepressants: amitriptyline, venlafaxine o β-Blockers: atenolol, nadolol o Triptans: naratriptan, zolmitriptan for short-term menstrually associated migraine prevention
European Federation of Neurological Societies: **Guideline on the Drug Treatment of Migraine - Revised Report of an European Federation of Neurological Societies Task Force (2009)**[58]	· Prophylactic drugs for the treatment of migraine with good efficacy and tolerability and evidence of efficacy are β-blockers, calcium-channel blockers, antiepileptic drugs, NSAIDs, antidepressants, and miscellaneous drugs. · The use of all these drugs is based on empirical data rather than on proven pathophysiological concepts. · There is no commonly accepted indication for starting a prophylactic treatment. Prophylactic drug treatment of migraine should be considered and discussed with the patient when 1) the quality of life, business duties, or school attendance are severely impaired; 2) frequency of attacks per month is two or higher; 3) migraine attacks do not respond to acute drug treatment; or 4) frequent, very long, or uncomfortable auras occur. · The recommended drugs of first choice are β-blockers (metoprolol or propranolol), calcium-channel blockers (flunarizine), and antiepileptic drugs (valproic acid or topiramate). · Drugs of second choice include amitriptyline, venlafaxine, naproxen, and bisoprolol. · Drugs of third choice include acetylsalicylic acid, gabapentin, magnesium, riboflavin, coenzyme Q10, candesartan, lisinopril, and methylsergide. · β-blockers are clearly effective in migraine prophylaxis and very well studied. The best evidence has been obtained for metoprolol and propranolol. Bisoprolol, timolol and atenolol might be effective, but evidence is less convincing compared with propranolol and metoprolol.

Clinical Guideline	Recommendations
	· The calcium-channel blocker, flunarizine, has been shown to be effective in migraine prophylaxis in several studies. · Valproic acid and topiramate are two antiepileptic drugs with evidence of efficacy in more than one placebo-controlled trial. The efficacy rates are comparable to those of metoprolol, propranolol, and flunarizine. Topiramate is also efficacious in the prophylaxis of chronic migraine and may have some effect in migraine with medication overuse.
National Cancer Institute: **Pheochromocytoma and Paraganglioma Treatment (PDQ®) (2013)**[59]	· If tachycardia develops or if blood pressure control is not optimal with α-adrenergic blockade, a β-blocker (e.g., metoprolol or propranolol) can be added, but only after α-blockade. · A β-blocker must never be initiated before α-blockade; doing so blocks β-blocker mediated vasodilation and results in unopposed α-blocker receptor mediated vasoconstriction, which can lead to a life-threatening crisis.
American Academy of Neurology: **Practice Parameter: Therapies for Essential Tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology (2005)**[60], **Evidence-based guideline update: Treatment of essential tremor (2011 update)**[61] **Reaffirmed April 2014**	· Propranolol and primidone are agents that are most commonly used to treat essential tremor (ET). · It is recommended that propranolol, long-acting propranolol, or primidone be offered to patients who want treatment for limb tremor in ET, depending on concurrent medical conditions and potential side effects. · It is recommended that either primidone or propranolol be used as initial therapy to treat limb tremor in ET. · It is recommended that atenolol and sotalol be considered for treatment of limb tremor associated with ET, and propranolol may be considered as a treatment option for head tremor in patients with ET. · Nadolol may be considered a treatment option for limb tremor associated with ET. · Pindolol is not recommended for treatment of limb tremor in ET. · Due to the lack of evidence, a recommendation regarding the use of metoprolol in the treatment of limb tremor in ET cannot be provided. · The combination of primidone and propranolol may be used to treat limb tremor when the use of a single agent does not adequately decrease tremor. · The dosages of propranolol and primidone may need to be increased after 12 months of therapy when treating limb tremor in ET. · Levetiracetam and 3,4-diaminopyridine should not be considered for treatment of limb tremor in ET. · Clinicians may choose not to consider flunarizine for treatment of limb tremor in ET. · The evidence is insufficient to make recommendations regarding the use of pregabalin, zonisamide, or clozapine

Conclusions

The beta-adrenergic blocking agents (β-blockers) are Food and Drug Administration (FDA)-approved for the treatment of angina, arrhythmias, essential tremor, heart failure, hypertension, hypertrophic aortic stenosis, migraine prophylaxis, myocardial infarction, and pheochromocytoma.[1-26] Agents that have a greater affinity for β1 receptors are considered to be cardioselective. These agents may be safer in patients with asthma, chronic obstructive pulmonary disease, and peripheral vascular disease because they produce less inhibition of β2 receptors, which mediate vasoconstriction and bronchospasm. Cardioselectivity is dose dependent; therefore, β2 blockade can occur at higher doses with these agents. Carvedilol and labetalol also block α-adrenergic receptors. [27-28] Current clinical guidelines identify β-blockers as effective in many indications with their place in therapy varying depending on indication and other patient specific factors.[29-61] Despite the extensive experience with β-blockers in clinical practice,

there have been no studies suggesting that any of these agents have major advantages or disadvantages in relation to the others for the treatment of many cardiovascular diseases. When any available β-blocker is titrated properly, it can be effective in patients with an arrhythmia, hypertension, or angina pectoris and other indications.[63-185]

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