

Drug Class Update: Beta Blockers, Oral

Date of Review: August 2022

Date of Last Review: May 2015

Dates of Literature Search: 01/01/2015-05/02/2022

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

To review and evaluate recent evidence and guideline recommendations for beta blockers approved for the treatment of hypertension, angina, heart failure, left ventricular dysfunction after myocardial infarction, arrhythmias, infantile hemangiomas, esophageal varices, or for migraine prophylaxis.

Research Questions:

1. For adult patients with hypertension, angina, recent myocardial infarction, heart failure, arrhythmias, bleeding esophageal varices, or migraines, do beta blocker drugs differ in efficacy or effectiveness?
2. For adult patients with hypertension, angina, recent myocardial infarction, heart failure, arrhythmias, bleeding esophageal varices, or migraines, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographic characteristics (i.e., age, race, ethnicity, gender), other medications (drug-drug interactions), or comorbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

Conclusions:

- Since the previous beta blocker literature scan, 5 high-quality systematic reviews have been published which assess the comparative safety and efficacy of beta blockers in hypertension, heart failure, migraine prophylaxis, and infantile hemangiomas.¹⁻⁵ Seven guidelines addressing the therapeutic use of beta blockers in hypertension, chronic coronary disease, gestational hypertension, heart failure, atrial fibrillation, ascites in patients with cirrhosis, and infantile angioma have been published or updated.⁶⁻¹²

Systematic Reviews

- A 2017 systematic review evaluated treatment of hypertension to assist in the update of an American College of Cardiology (ACC)/American Heart Association (AHA) clinical practice guideline.¹ No class of medications including angiotensin converting enzyme inhibitor (ACEIs), angiotensin-II receptor blocker (ARBs), calcium channel blocker (CCBs) or beta blockers, was significantly better than thiazide diuretics as a first-line therapy for any outcome related to hypertension.¹ Compared to beta-blockers, thiazides were associated with a lower risk of stroke, all-cause mortality, cardiovascular mortality, and cardiovascular events.¹

- A 2021 Cochrane review assessed the safety and efficacy of beta blockers in patients without heart failure in the non-acute phase after myocardial infarction (MI).² The meta-analyses show that beta blockers compared with placebo or no intervention probably reduce risk of all-cause mortality (risk ratio [RR] 0.81, 97.5% confidence interval [CI] 0.73 to 0.90; moderate-certainty evidence) and MI (RR 0.76, 98% CI 0.69 to 0.88; moderate-certainty evidence) in this population.² Beta blockers compared with placebo or no intervention may reduce the risks of major cardiovascular events (RR 0.72, 97.5% CI 0.69 to 0.84; low-certainty evidence) and cardiovascular mortality (RR 0.73, 98% CI 0.68 to 0.85; $I^2 = 47%$; low-certainty evidence).²
- A 2021 Cochrane review assessed the effects of beta blockers, ACEIs, ARBs, angiotensin receptor neprilysin inhibitors (ARNIs), and mineralocorticoid receptor antagonists (MRAs) in people with heart failure with preserved ejection fraction (HFpEF).³ A possible reduction in cardiovascular mortality was observed with beta blockers (RR 0.78, 95% CI 0.62 to 0.99; low-certainty evidence).³ There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; low-certainty evidence).³ Based on low quality evidence, the effects of beta blockers on heart failure hospitalization, and quality of life in patients with HFpEF remain uncertain.³
- A 2019 systematic review and meta-analysis assessed the efficacy of beta blockers in preventing migraine and tension-type headaches.⁴ High-quality evidence shows propranolol 160 mg to 240 mg once daily is effective in reducing episodic migraine frequency compared to placebo.⁴ At 8 weeks patients with migraine headaches experienced an average reduction of 1.5 headaches per month (95% CI -2.3 to -0.65) with propranolol compared with placebo.⁴ In 3 trials, metoprolol also reduced headache frequency, though the reduction was less than 1 headache a month.⁴ Conclusions regarding the efficacy of other beta blockers is less certain, as most were studied in only one trial.⁴ Atenolol, bisoprolol and timolol have weak evidence of benefit.⁴ Acebutolol and nadolol appear to be ineffective in migraine prophylaxis.⁴
- A 2018 Cochrane review assessed the effects of oral propranolol versus topical timolol versus placebo and for the management of infantile hemangiomas in children.⁵ There is moderate-quality evidence that, when compared with placebo, oral propranolol is probably beneficial in terms of complete or almost complete clearance and probably reduces hemangioma volume more than placebo.⁵ There is low-quality evidence which assessed a difference in short- or long-term adverse events between oral propranolol and placebo, which made definitive conclusions difficult.⁵ Low-quality evidence indicates that topical timolol may reduce infantile hemangioma redness more than placebo, with possibly no accompanying cardiovascular events, although no other safety data were assessed for this comparison.⁵ There was no evidence of a difference between oral propranolol and topical timolol maleate in their ability to generate a 50% or greater reduction in infantile hemangioma size, based on low-quality evidence.⁵ Very low-quality evidence about adverse events made it difficult to draw conclusions about the comparative safety of oral propranolol versus topical timolol in managing infantile hemangioma.⁵

Clinical Practice Guidelines

- The 2020 International Society of Hypertension (IHS) guideline was developed to provide recommendations for the management of hypertension in adults, aged 18 years and older.⁶ In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's systolic blood pressure (SBP) in the office or clinic is 140 mmHg or higher and/or their diastolic blood pressure (DBP) is 90 mmHg or higher, following repeated examination.⁶ Beta blockers should be considered to manage hypertension when there is a specific indication for their use (e.g. heart failure, angina, post-MI, atrial fibrillation, or in hypertensive patients planning pregnancy or currently pregnant).⁶
- The 2020 American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin addressed optimal antihypertensive treatment for patients with gestational hypertension or preeclampsia.⁷ Antihypertensive treatment should be initiated for severe hypertension (SBP of 160 mm Hg or more or DBP of 110 mm Hg or more, or both) that is confirmed as persistent.⁷ Oral labetalol and CCBs have been commonly used.⁷ One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/day).⁷
- The 2019 European Society of Cardiology (ESC) guidance for management of chronic coronary syndromes updated 2013 guidance focused on management of stable coronary artery disease (CAD).⁸

- ◆ First-line treatment for angina/ischemia relief is with beta blockers or non-dihydropyridine CCBs that control heart rate and symptoms (Class 1 recommendation; high-quality evidence).⁸
- The 2021 ESC guidance on heart failure includes recommendations regarding the use of beta blockers to treat different heart failure stages and co-morbidities associated with heart failure as follows:
 - ◆ A beta blocker may be considered in patients with mild heart failure and reduced ejection fraction (HFrEF) (e.g. patients with an ejection fraction 40% to 49%) to reduce the risk of heart failure hospitalization and death (Class 2B recommendation; low-quality evidence).⁹
 - ◆ A beta blocker is recommended for patients with stable heart failure with reduced ejection fraction (HFrEF) to reduce the risk of heart failure hospitalization and death (Class 1 recommendation: high-quality evidence).⁹
 - ◆ Beta blockers should be considered for short- and long-term rate control in patients with heart failure and atrial fibrillation (Class 2A recommendation: moderate-quality evidence).⁹
- The 2020 Canadian Cardiovascular Society (CCS) and Canadian Heart Rhythm Society (CHRS) guideline on management of atrial fibrillation is an update of 2010 guidance.¹⁰ Beta blockers are preferred in patients with acute coronary syndrome who require acute rate control.¹⁰ Intravenous rate control agents might be initially considered if the patient is not hemodynamically stable.¹⁰
 - ◆ Either beta blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for atrial fibrillation rate control in patients without significant left ventricular (LV) dysfunction (e.g., patients with an ejection fraction greater than 40%). (strong recommendation; moderate-quality evidence).¹⁰
 - ◆ Beta blockers bisoprolol, carvedilol and metoprolol are first-line agents for rate control of hemodynamically stable atrial fibrillation in the acute care setting in patients with significant LV dysfunction (e.g., patients with an ejection fraction 40% or less). (strong recommendation; moderate-quality evidence).¹⁰
- In 2021 the British Society of Gastroenterology in collaboration with British Association for the Study of the Liver updated 2007 guidance on the management of ascites in cirrhosis.¹¹ The use of beta blockers in ascites is a very small component of the overall management strategies. The portal pressure-lowering effects of non-selective beta blockers have been known to be beneficial in patients with ascites for three decades.¹¹ Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.¹¹
 - ◆ Refractory ascites should not be viewed as a contraindication to a non-selective beta blocker. (strong recommendation; moderate-quality evidence).¹¹
 - ◆ Patients with refractory ascites who are taking a non-selective beta-blocker should be monitored closely, and dose reduction or discontinuation may be appropriate in those who develop hypotension or acute/progressive renal dysfunction. (strong recommendation; moderate-quality evidence).¹¹
- In 2019, the American Academy of Pediatrics (AAP) published clinical practice guidelines on the management of infantile hemangioma.¹² Pharmacotherapy recommendations are as follows:
 - ◆ Use propranolol as the first-line agent for infantile hemangioma requiring systemic treatment (strong recommendation; high-quality evidence).¹²
 - ◆ May prescribe oral prednisolone or prednisone to treat infantile hemangioma if there are contraindications or inadequate response to oral propranolol (moderate recommendation; moderate-quality evidence).¹²
 - ◆ May prescribe topical timolol maleate as a therapy for thin and/or superficial infantile hemangioma (moderate recommendation; moderate-quality evidence).¹²

- No subgroups of patients based on demographic characteristics (i.e., age, race, ethnicity, gender), other medications (drug-drug interactions) have been identified for which one beta-blocker is more effective or associated with fewer adverse effects. However, beta blockers are only appropriate first-line agents in hypertension when treating specific, compelling indications including stable ischemic heart disease, atrial fibrillation, or heart failure.^{8,9} Three beta blockers, bisoprolol, carvedilol, and extended-release metoprolol succinate, have been shown to reduce mortality and morbidity in patients with HFrEF.⁹ A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI to manage atrial fibrillation.¹⁰ Acebutolol is no longer included as an appropriate beta blocker to initiate after MI. Labetalol is the preferred oral beta-blocker for managing gestational hypertension.¹³ Finally, propranolol has demonstrated efficacy in migraine prophylaxis⁴ and treatment of infantile hemangioma.^{5,12} Topical timolol is also effective in treatment of thin (less than 1 mm), superficial infantile hemangioma.¹²

Recommendations:

- Based on current evidence, make acebutolol non-preferred. Make at least one form of extended-release 24 hour propranolol capsule, at least one form of generic propranolol oral solution, and nadolol preferred on the PDL.
- After review drug costs in the executive session, make propranolol SA 24 hour capsules, generic oral propranolol solution, and nadolol tabs preferred.
- Make Hemangeol oral solution open access up to 6 months of age for treatment of infantile hemangioma.

Summary of Prior Reviews and Current Policy:

- The beta blocker drug class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the May 2015 meeting. A Drug Effectiveness Review Project (DERP) scan was used to identify any new comparative research. All of the beta blockers reviewed were effective in the treatment of hypertension, but there was no evidence of differences between beta blockers for blood pressure control, survival, or quality of life.
- Based on previous recommendations, at least one of the following drugs with evidence of effectiveness in moderate to severe chronic heart failure should be preferred on the Preferred Drug List (PDL): carvedilol or metoprolol succinate. In addition, based on previous recommendations, at least one of the following drugs with evidence of effectiveness in recent myocardial infarction (MI) should be preferred on the PDL: acebutolol, carvedilol, metoprolol tartrate, propranolol or timolol. Finally, based on previous recommendations, at least one of the following drugs with evidence of effectiveness for reducing esophageal variceal bleeds should be preferred on the PDL: atenolol, nadolol, propranolol or extended-release propranolol.
- **Appendix 1** summarizes the current preferred beta blocker status on the PDL which includes: acebutolol, atenolol, carvedilol, labetalol, metoprolol succinate, metoprolol tartrate, and propranolol.
- In the first quarter of 2022, 97% of the beta blocker utilization was for preferred agents (e.g., propranolol, metoprolol succinate, carvedilol, metoprolol tartrate, atenolol, and labetalol). The remainder of the utilization was for non-preferred agents including sotalol, bisoprolol, nadolol, extended-release propranolol, and propranolol solution.

Background:

Adrenergic beta antagonists, commonly called beta blockers, refer to a group of drugs with diverse pharmacodynamic and pharmacokinetic properties.¹⁴ Beta blockers competitively inhibit beta receptors and thus modulate sympathetic nervous system activity.¹⁵ They act via multiple pathways, limiting the effects of catecholamine excess, affecting inotropy and chronotropy, providing anti-arrhythmic and anti-ischemic effects and inhibiting renin release.¹⁶ The primary therapeutic uses of beta blockers include: hypertension, angina, post-MI, arrhythmias, and heart failure.¹⁷ Beta blockers can be distinguished by the following properties: selectivity for beta-1 and beta-2 receptors; intrinsic sympathomimetic activity; blockade of alpha receptors; differences in lipid solubility; capacity to induce vasodilation; and pharmacokinetic parameters.¹⁸ Beta adrenergic receptors are present in many body systems including the heart, blood vessels, lungs,

kidneys, and nervous system. There are 3 main classes of beta-receptors: beta-1, beta-2, and beta-3. Beta-1 selective (cardioselective) receptor blockers act mainly on the myocardium with less of an effect on the bronchial or vascular smooth muscle tissues, where beta-2 receptors are present.¹⁷ In patients with bronchospastic reactive airway disease requiring a beta blocker, a cardioselective agent (e.g., atenolol, betaxolol, bisoprolol, metoprolol) is preferred.¹⁹ Beta-1 selective receptor blockers have no intrinsic sympathomimetic activity or alpha-blocking effects. Non-selective beta blockers may decrease cardiac output due to a decrease in cardiac contractility, heart rate and slight increase in peripheral resistance.¹⁷ Beta blockers with partial beta-agonistic activity (e.g., pindolol, acebutolol) or those possessing some alpha-blocking activity (e.g., carvedilol, labetalol) can lower peripheral vascular resistance.¹⁷

On the basis of their pharmacokinetic properties, beta blockers can be classified into two broad categories: those eliminated by hepatic metabolism and those excreted unchanged by the kidney.²⁰ Hepatically metabolized drugs such as propranolol and metoprolol, are lipid-soluble, almost completely absorbed by the small intestine, and largely metabolized by the liver.²⁰ They enter the central nervous system (CNS) in high concentrations, possibly resulting in an increased incidence of CNS side effects.²⁰ In contrast, renally eliminated beta blockers, such as atenolol and sotalol, are more water soluble, incompletely absorbed through the gut, eliminated unchanged by the kidney, and do not as readily enter the CNS.^{20,21} Renally eliminated beta blockers show less variance in bioavailability and have longer plasma half-lives.²¹ A pharmacodynamic and pharmacokinetic comparison of oral beta blockers is presented in **Table 1**.

Table 1. Beta Blocker Pharmacokinetic and Pharmacodynamic Comparisons^{22,23}

Drug Name	Indications	Primary Site of Metabolism	Mixed Alpha- and Beta-Blocker	Cardioselective (Beta-1 selective)	ISA
Acebutolol	Hypertension; arrhythmias	Hepatic		X	X
Atenolol	Angina; hypertension	Renal		X	
Betaxolol	Hypertension	Renal		X	
Bisoprolol	Hypertension, heart failure, post-MI	Hepatic/Renal		X	
Carvedilol	Heart failure; hypertension; post-MI	Hepatic	X		
Labetalol	Hypertension	Hepatic	X		
Metoprolol	Angina; heart failure; hypertension; post-MI	Hepatic		X	
Nadolol	Angina pectoris; hypertension	Renal			
Nebivolol	Hypertension	Hepatic		X	
Pindolol	Hypertension	Hepatic			X
Propranolol	Angina; infantile hemangioma; arrhythmias; essential tremor; hypertension; migraine prophylaxis; pheochromocytoma, post-MI	Hepatic			
Sotalol	Arrhythmias	Renal			
Timolol	Hypertension, post-MI	Hepatic			

Abbreviations: ISA = intrinsic sympathomimetic activity; MI = myocardial infarction

For patients with hypertension but without compelling indications, a beta blocker should not be used as the initial first-line agent.¹⁹ Clinical trial data and meta-analyses suggest that hypertension treatment with a beta blocker may reduce cardiovascular events better than placebo, but not to the extent that an ACEI, ARB, CCB, or thiazide diuretic can achieve.¹⁹ A beta blocker is only an appropriate first-line agent in hypertension when treating specific, compelling indications such as stable ischemic heart disease or heart failure.^{8,9}

Beta blockers should be used for the treatment of hypertension in patients with stable ischemic heart disease who have reduced left ventricular ejection fraction (LVEF) after MI.¹⁹ In these patients, beta blockers decrease myocardial ischemia, reinfarction, and the frequency of complex ventricular dysrhythmias.²⁴ In randomized long-term trials, use of beta blockers after MI reduced all-cause mortality by 23%.¹⁹ The protective benefit in asymptomatic patients with depressed LVEF without a history of MI is less well established and lacks placebo-controlled trials.²⁵ A beta blocker without intrinsic sympathomimetic activity such as extended-release metoprolol succinate, bisoprolol, or carvedilol, should be initiated in the setting of an acute MI.²⁴

Hypertension in pregnancy is a condition affecting 5–10% of pregnancies worldwide.⁶ Hypertension in pregnancy includes the following conditions: persistent BP greater than 140/90 mmHg in gestational hypertension; pre-existing hypertension with superimposed gestational hypertension; and hypertension with subclinical hypertension mediated organ damage at any time during pregnancy.⁶ Maternal risks include placental abruption, stroke, multiple organ failure (liver, kidney), and disseminated vascular coagulation.⁶ Fetal risks include intrauterine growth retardation, preterm birth, and intrauterine death.⁶ When antihypertensive drug therapy should be initiated varies by guideline. ACOG recommends starting drug therapy when blood pressure is 160/110 mm Hg or greater.⁷ International societies recommend beginning drug treatment when blood pressure is greater than 140/90 mm Hg.⁶ However, the benefit from normalization of blood pressure treatment for pregnant women, coupled with theoretical concerns for fetal well-being from a reduction *in utero* placental perfusion and *in utero* exposure to antihypertensive medication has some controversy in clinical practice.²⁶ Initial drug therapy is monotherapy with labetalol or methyldopa.²⁶ Some, but not all, clinical guidelines support the use of oral nifedipine as initial therapy.²⁶ These therapeutic options are based on small individual trials and are advocated by national and international clinical practice guidelines.²⁶ Some observational studies have associated beta blocker treatment, including labetalol, with an increased risk for birthing small-for-gestational-age infants, although the study investigators did not adjust for treatment indication and severity of maternal disease.²⁶ Metoprolol and pindolol are considered acceptable alternatives to labetalol based on limited data in pregnant patients.²⁷ Propranolol and other non-elective beta blockers should be avoided as they may promote uterine irritability through beta-2 receptor blockade.²⁷ Atenolol has been associated with slightly lower placental and fetal weight at delivery when used early in pregnancy and should be avoided if an effective drug with a better safety profile is available.^{28,29}

Beta blockers are one of the main classes of medications used for treating patients with HFrEF, defined as LVEF of 40% or less. Patients with heart failure with no or minimal evidence of volume overload should be treated with one of the following beta blockers with established clinical benefits in randomized trials: carvedilol, extended release metoprolol succinate, or bisoprolol.¹⁷ In patients with HFrEF, these 3 beta-blockers have been shown to reduce morbidity and mortality from cardiovascular disease, reduce hospitalization rates, and improve symptoms.³⁰ The favorable findings with these 3 beta blockers should not be considered a beta blocker class effect in HFrEF.³¹ Other beta blockers are not recommended for use in patients with HFrEF.³¹ Clinical trials have shown that beta blockers should be prescribed to all patients when HFrEF is diagnosed, including in-hospital, unless contraindicated or not tolerated.³¹ The benefits of beta blockers were observed in patients with or without CAD, and in patients with or without diabetes, older patients, as well as in women and across racial and ethnic groups but not in patients with atrial fibrillation.³¹ Even if symptoms do not improve, long-term treatment should be maintained to reduce the risk of major cardiovascular events.³¹

The use of beta blockers in ascites is a very small component of the overall management strategies. The portal pressure-lowering effects of non-selective beta blockers (e.g., carvedilol, propranolol, nadolol) have been known to be beneficial in patients with ascites for three decades.¹¹ A 1991 meta-analysis of trial data demonstrated that non-selective beta blockers reduce the likelihood of first variceal hemorrhage in the ascites subgroup, while in Child's Pugh B and C cirrhosis the addition of non-selective beta blockers to band ligation results in less variceal rebleeding and superior survival.¹¹ Proven hemodynamic response to non-selective beta blockers (drop in hepatic venous pressure gradient (HVPG) of 10 to 20% or more from baseline, or to less than 12 mm Hg) has been linked with a lower probability of the development of ascites; and in patients already with ascites, a lower probability of refractory ascites and hepatorenal syndrome.¹¹ However, it remains possible that non-response in this context is simply a surrogate marker for disease severity.¹¹ Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.¹¹

Infantile hemangiomas (previously known as strawberry birthmarks) are the most common vascular tumors among children, occurring in 3% to 10% of infants.⁵ These benign vascular tumors are usually uncomplicated and tend to regress spontaneously.⁵ However, when hemangiomas occur in high-risk areas, such as near the eyes, throat, or nose, impairing their function, or when complications develop, intervention may be necessary.⁵ The skin covering hemangiomas may become ulcerated, exposing the underlying blood vessels and making them more liable to bleed from minor trauma and become infected.⁵ Although most hemangiomas are self-limited and do not need treatment, some indications for treatment include the following: high-output cardiac failure, bleeding, ulceration, risk of permanent disfigurement, or airway or visual obstruction.⁵ Infantile hemangiomas appear more commonly among White persons, being evident in up to 12% of all White children.⁵ Infantile hemangiomas affect females in a ratio of 3:1.⁵ Sixty per cent of infantile hemangiomas are located in the head and neck area, whereas 25% occur on the trunk and 15% on the extremities.⁵ A chance observation of an antiproliferative effect of propranolol on infantile hemangioma was described in 2015.⁵ This drug has showed a highly effective profile with tolerable adverse events, in comparison with previous recommended interventions used for infantile hemangioma (e.g. steroids, interferon, chemotherapy).⁵ Minimal side effects were reported with propranolol, and the response rate approached 100%.⁵ Propranolol is now the first-line treatment for infantile hemangioma and has been approved for this indication.⁵

Most adverse drug reactions experienced with the use of beta blockers are an extension of their pharmacologic activity.¹⁵ Beta blockers can cause bradycardia, atrioventricular block and symptomatic hypotension, especially in patients with sinus or atrioventricular node dysfunction, and are contraindicated in severe asthma because of the risk of life-threatening bronchospasm.¹⁶ Central nervous system adverse drug effects like fatigue, depression, insomnia, and general malaise are usually mild but are among the most common reasons for treatment discontinuation.¹⁵ In addition, most beta blockers negatively influence glucose or lipid metabolism.³² Beta blockers are absolutely contraindicated in patients with pre-existing bradycardia, second or third-degree atrioventricular block, a history of uncontrolled reactive airway disease (e.g., severe asthma), severe peripheral arterial disease (e.g., critical limb ischemia), hypotension, HFrEF with unstable fluid status, and patients with diabetes who have frequent episodes of hypoglycemia.¹⁵ If beta blocker therapy needs to be discontinued, doses should be slowly tapered over 2 to 3 weeks to prevent abrupt withdrawal.¹⁵

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

American College of Cardiology/American Heart Association Task Force: Hypertension Treatment

A 2017 systematic review evaluated literature focused on detection, evaluation, and treatment of hypertension to assist in the update of an ACC/AHA clinical practice guideline.¹ The research question most pertinent for the current beta blocker class update addresses how various antihypertensive drug classes differ in their benefits and harms compared with each other as first line-therapy for adults with hypertension.¹ Literature was searched through 2015.¹ Study population criteria required that study participants be adults 18 years of age and older with primary hypertension or hypertension due to chronic kidney disease.¹ The study interventions must have used thiazides, ACEIs, ARBs, CCBs, or beta blockers.¹ Comparators were the same as described for the interventions as long as they represented a different class of antihypertensive medication than the intervention.¹ There were 8 outcome criteria evaluated in the review: all-cause mortality, cardiovascular mortality, congestive heart failure (CHF), stroke, MI, composite cardiovascular events, major adverse cardiac events, and renal outcomes.¹ Fifty-eight RCTs (n=152,379 with 3.5 years of follow-up) met inclusion criteria.¹ Fourteen trials included a thiazide arm, 25 RCTs had an ACEI arm, 9 RCTs had an ARB arm, 28 RCTs had a CCB arm, and 10 RCTs had a beta-blocker arm.¹ The mean age of enrolled populations ranged from 47 to 69 years, and approximately 50% of participants were women.¹ Overall, the studies included in the analyses showed low or unclear risk of bias.¹ There appeared to be publication bias against studies with longer follow-up and null findings.¹ The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) trial contributed the largest number of participants randomized to beta-blockers for assessment of all-cause mortality, cardiovascular mortality, MI, and heart failure.¹

Random-effects Bayesian network meta-analyses were conducted to compare multiple antihypertensive treatments within the same statistical model.¹ Compared with thiazides, the relative risks of all-cause mortality were 1.0 (95% CI 0.95 to 1.1) for ACEIs; 0.99 (95% CI 0.88 to 1.1) for ARBs; 1.1 (95% CI 0.98 to 1.2) for beta-blockers; and 0.97 (95% CI 0.90 to 1.1) for CCBs.¹ Compared with thiazides, the relative risks of cardiovascular mortality were 1.1 (95% CI 0.92 to 1.3) for ACEIs; 1.1 (95% CI 0.87 to 1.5) for ARBs; 1.2 (95% CI 0.98 to 1.4) for beta-blockers; and 1.0 (95% CI 0.86 to 1.2) for CCBs.¹ Also, the risk of cardiovascular mortality was higher (but not statistically significant) for beta blockers compared with CCBs (RR 1.2; 95% CI 0.98 to 1.4).¹ Compared with thiazides, the relative risks of stroke were 1.1 (95% CI 0.98 to 1.4) for ACEIs; 1.1 (95% CI 0.88 to 1.4) for ARBs; 1.3 (95% CI 1.1 to 1.6) for beta-blockers; and 0.96 (95% CI 0.83 to 1.2) for CCBs.¹ There was also an increased, but not statistically significant risk of stroke for ACEIs and beta-blockers compared with CCBs (RR 1.2; 95% CI 1.0 to 1.4 and RR 1.4; 95% C 1.1 to 1.7, respectively).¹ Compared with thiazides, the relative risks of cardiovascular events were 1.1 (95% CI 0.96 to 1.3) for ACEIs; 1 (95% CI 0.89 to 1.2) for ARBs; 1.2 (95% CI 1.0 to 1.4) for beta blockers; and 1.1 (95% CI 0.98 to 1.2) for CCBs.¹ The risk of cardiovascular events was reduced (but not statistically significant) for ARBs compared with beta blockers (RR 0.88; 95% CI 0.78 to 1.0).¹ There were also no statistically significant differences between drug classes in risk of adverse renal outcomes.¹

To investigate whether these results were consistent by race, the authors conducted stratified analyses among studies with predominantly Black study participants (defined as studies reporting subgroup analysis in Blacks or having populations with at least 85% Black participants) or which published race-specific analyses.¹ No significant differences were observed in all-cause mortality, cardiovascular mortality, MI, CHF, cardiovascular events, or renal outcomes among Blacks between any of the drug classes.¹ Effects by multiple subgroups of interest including age, race, sex, and diabetes mellitus status were also assessed.¹ No significant effects were identified, likely due to the relatively few studies for each class-to-class comparison with published data available for these analyses.¹ Therefore, these findings should be interpreted with caution.¹

In summary, SBP lowering to a target of less than 130 mm Hg may reduce the risk of several important outcomes including risk of stroke, CHF, major cardiovascular events, and mortality.¹ No other class of antihypertensives (i.e., ACEIs, ARBs, CCBs, or beta blockers) was significantly better than thiazide diuretics as a first-line therapy for any outcome related to hypertension.¹ Compared to beta blockers, thiazides were associated with a lower risk of stroke and cardiovascular events.¹

Cochrane: Beta Blockers In Patients Without Heart Failure After Myocardial Infarction

A 2021 Cochrane review assessed the safety and efficacy of beta blockers in patients without heart failure in the non-acute phase after MI.² Literature was searched through February 2021 to identify all RCTs assessing effects of beta blockers versus control (placebo or no treatment) in patients without heart failure after MI.² Primary outcomes were all-cause mortality, serious adverse events (SAEs), and major cardiovascular events (composite of cardiovascular mortality and non-fatal MI).² Secondary outcomes were quality of life, angina, cardiovascular mortality, and MI during follow-up.² Twenty-five RCTs (n=22,423) met inclusion criteria.² All trials and outcomes were at high risk of bias.²

The meta-analyses show that beta blockers compared with placebo or no intervention probably reduce the risks of all-cause mortality (RR 0.81, 97.5% CI 0.73 to 0.90; $I^2 = 15\%$; 22,085 participants, 21 trials; moderate-certainty evidence) and MI (RR 0.76, 98% CI 0.69 to 0.88; $I^2 = 0\%$; 19,606 participants, 19 trials; moderate-certainty evidence).² Beta blockers compared with placebo or no intervention may reduce the risks of major cardiovascular events (RR 0.72, 97.5% CI 0.69 to 0.84; 14,994 participants, 15 trials; low-certainty evidence) and cardiovascular mortality (RR 0.73, 98% CI 0.68 to 0.85; $I^2 = 47\%$; 21,763 participants, 19 trials; low-certainty evidence).² Evidence seems to suggest that beta blockers versus placebo or no treatment may result in a minimum reduction of 10% in RR for risks of all-cause mortality, major cardiovascular events, cardiovascular mortality, and MI.² However, beta blockers compared with placebo or no intervention may not affect the risk of angina (RR 1.04, 98% CI 0.93 to 1.13; $I^2 = 0\%$; 7115 participants, 5 trials; low-certainty evidence).² No trials provided data on SAEs or quality of life.²

Cochrane: Beta Blockers And Inhibitors Of The Renin-Angiotensin-Aldosterone System For Chronic Heart Failure With Preserved Ejection Fraction

A 2021 Cochrane review assessed the effects of beta blockers, ACEIs, ARBs, ARNIs, and MRAs in people with HFpEF.³ Literature was searched through May 2020 to identify RCTs with a parallel group design which enrolled adults with HFpEF, defined by LVEF greater than 40%.³ Forty-one RCTs met inclusion criteria.³ The risk of bias in trials was frequently unclear and only five studies had a low risk of bias in all domains.³

For the purposes of this drug class update, the focus will be on the 10 trials (n=3087) which evaluated beta blockers.³ Five studies used a placebo comparator and in 5 RCTs, the comparator was usual care.³ The mean age of participants ranged from 30 years to 81 years.³ A possible reduction in cardiovascular mortality was observed with beta blockers (RR 0.78, 95% CI 0.62 to 0.99; number needed to treat (NNT) 25; 1046 participants; 3 studies); however, the certainty of evidence was low due to the small trial sizes and uncertainty about the study methodology.³ There may be little to no effect on all-cause mortality (RR 0.82, 95% CI 0.67 to 1.00; 1105 participants; 4 studies; low-certainty evidence).³ The effects of beta blockers on heart failure hospitalization and quality of life in patients with HFpEF remain uncertain.³

Beta Blockers For The Prevention Of Headache In Adults

The purpose of a 2019 systematic review and meta-analysis was to assess the efficacy of beta blockers in preventing migraine and tension-type headache.⁴ Literature was searched through August 2018.⁴ One hundred eight RCTs ranging from 4 to 64 weeks in duration met inclusion criteria.⁴ Fifty RCTs were placebo-controlled and 58 RCTs were comparative effectiveness trials.⁴ The average age of patients was 37 years and 77% of participants were women.⁴ Ten different beta blockers were studied. Propranolol 80 mg to 240 mg per day (n=74) and metoprolol 100 mg to 200 mg per day (n=21) were the most commonly evaluated beta

blockers.⁴ Atenolol, nadolol, pindolol and timolol had 2 studies each.⁴ Compared to placebo, propranolol reduced episodic migraine headaches by 1.5 headaches per month at 8 weeks (95% CI -2.3 to -0.65) and was more likely to reduce headaches by 50% (RR 1.4, 95% CI 1.1 to 1.7).²² Studies had a number of quality issues including high drop-out rates (16%), lack of intention to treat analysis (76%), inadequate sequence generation (83%), lack of evidence of concealed allocation (90%) and inadequate blinding (60%).⁴ Trials comparing beta blockers to other interventions were largely single trials.⁴

The primary outcome of interest was number of headaches per month.⁴ Among patients with episodic migraines, the average number of headaches at baseline was 4.9 headaches per month.⁴ The most studied beta blocker was propranolol, which was more effective than placebo at 8 and 12 weeks (8 weeks: -1.5 headaches/month, 95% CI -2.3 to -0.65); 12 weeks: -1.2 headaches/month, 95% CI -1.8 to -0.60).⁴ Propranolol outcomes at 8 and 12 weeks were both graded as high-quality evidence.⁴ The recommended dose of propranolol extended release for migraine prophylaxis is an initial dose of 80 mg once daily, and gradually increased to the usual effective dose of 160 mg to 240 mg once daily.³³ The propranolol immediate release formulation may also be used, but the daily dose must be administered in 3 to 4 divided doses per day.³⁴ Propranolol was comparable to other medications known to be effective in migraine prophylaxis including topiramate and valproate.⁴ Other beta blockers that were more effective than placebo at 8 weeks included bisoprolol (-0.70 headaches/month, 95% CI -1.4 to -0.05, low quality), metoprolol (-0.86 headaches/month, 95% CI -1.4 to -0.34, moderate quality) and timolol (-0.77 headaches/month, 95% CI -1.4 to -0.12, moderate quality).⁴ Two beta blockers, acebutolol and bisoprolol, did not significantly reduce headache frequency in single trials.⁴

There were 4 trials that evaluated propranolol to an active comparator (e.g., nortriptyline, topiramate, and valproic acid) for chronic migraine headaches.⁴ Propranolol was more likely to reduce chronic migraine headaches by at least 50% (RR 2.0, 95% CI 1.0 to 4.3).⁴ There was only one trial of beta blockers for tension-type headache, comparing the combination of pindolol and amitriptyline to placebo and to amitriptyline alone.⁴ The combination of pindolol and amitriptyline was more effective than placebo at reducing headache frequency at 4 and 8 weeks and in reducing headaches by at least 50% (RR 3.8, 95% CI 1.5 to 9.3), but equally effective with amitriptyline.⁴

Participants on beta blockers were more likely to experience side effects than those on placebo (RR 1.2, 95% CI 1.0 to 1.4), though they were not more likely to withdraw from therapy (RR 0.99, 95% CI 0.83 to 1.2).⁴ Specific side effects more common with beta blockers included dizziness (RR 1.5, 95% CI 1.0 to 2.3) and fatigue (RR 1.5, 95% CI 1.2 to 2.0).⁴

In summary, there is high quality evidence that compared to placebo, propranolol was effective in reducing episodic migraine frequency.⁴ Other comparisons were rated as low-quality based on only including single trials, which made definitive conclusions about comparative effectiveness impossible.⁴ There were relatively few trials examining beta blocker effectiveness for chronic migraine or tension-type headache though there was limited evidence of benefit.⁴ Conclusions regarding the efficacy of other beta blockers is less certain, as most were studied in just one trial each.⁴ Atenolol, bisoprolol and timolol had weak evidence of benefit.⁴ Acebutolol and nadolol appeared to be ineffective in migraine prophylaxis.⁴

Cochrane: Interventions For Infantile Hemangiomas

A 2018 Cochrane review updated a 2011 review which assessed the effects of interventions for the management of infantile hemangiomas in children.⁵ The literature search for RCTs of all types of interventions in children with single or multiple infantile hemangiomas was completed in February 2017.⁵ Twenty-eight RCTs, with a total of 1728 participants, assessing 12 different interventions, including lasers, beta blockers (e.g. propranolol, timolol maleate), radiation therapy, and steroids (oral prednisolone) were identified.⁵ Comparators included placebo, an active monitoring approach, sham radiation, and interventions given alone or in combination.⁵ Studies were conducted in a number of countries, including Canada, China, Egypt, France, and Australia.⁵ Primary outcomes included clearance of the hemangioma, as assessed by the clinician at any follow-up: proportion of children with lesions completely cleared or with minimal residual signs

(defined as faint macular erythema with no palpable component) from baseline to six-month follow-up, and adverse events.⁵ Participant age ranged from 12 weeks to 13.4 years.⁵ Most studies (23/28) included a majority of females and different types of infantile hemangiomas.⁵ Duration of follow-up ranged from 7 days to 72 months.⁵ Most of the trials were at low risk of randomization errors, attritions, or selective reporting bias.⁵ The domains of allocation concealment and blinding were not clearly reported in general.⁵ Evidence was downgraded for issues related to risk of bias and imprecision.⁵ The 3 most important comparisons were: 1) oral propranolol versus placebo; 2) topical timolol versus placebo; and 3) oral propranolol versus topical timolol.

1) Oral Propranolol Versus Placebo

Compared with placebo, oral propranolol 3 mg/kg/day divided into 2 doses and administered for 6 months, probably improves clinician-assessed clearance (RR 16.61, 95% CI 4.22 to 65.34; 1 study; 156 children; moderate-quality evidence) and probably leads to a clinician-assessed reduction in mean hemangioma volume of 45.9% (95% CI 11.60% to 80.20%; 1 study; 40 children; moderate-quality evidence).⁵ No differences were identified in terms of short- or long-term SAEs (RR 1.05, 95% CI 0.33 to 3.39; 3 studies; 509 children; low-quality evidence), bronchospasm, hypoglycemia, or serious cardiovascular adverse events.⁵ There is moderate-quality evidence that, when compared with placebo, oral propranolol is probably beneficial in terms of complete or almost complete clearance and probably reduces hemangioma volume more than placebo.⁵ There is insufficient evidence to determine a difference in terms of short- or long-term adverse events between the groups (low-quality evidence).⁵ The single study was industry sponsored.⁵

2) Topical Timolol Maleate Versus Placebo

Topical timolol maleate is available in a 0.25% and 0.5% ophthalmic solution, as well as an extended release 0.5% gel-forming solution. Frequency and method of application have varied from once daily under occlusion to twice daily without occlusion; 1 to 2 drops have typically been used and are usually given for 2 to 6 months.⁵ The chance of reduction of redness, as a measure of clinician-assessed resolution, may be improved with topical timolol maleate 0.5% gel applied twice daily when compared with placebo (RR 8.11, 95% CI 1.09 to 60.09; 1 study; 41 children; low-quality evidence).⁵ Regarding short- or long-term serious cardiovascular events, no instances of bradycardia or hypotension were reported in either group (1 study; 41 children; low-quality evidence).⁵ No other safety data were assessed, and clearance was not measured.⁵ Low-quality evidence indicates that topical timolol maleate may reduce infantile hemangioma redness more than placebo, with possibly no accompanying cardiovascular events, although no other safety data were assessed for this comparison.⁵

3) Oral Propranolol Versus Topical Timolol Maleate

When topical timolol maleate (0.5% eye drops applied twice daily) was compared with oral propranolol (via a tablet taken once per day, at a 1.0 mg/kg dose), there was no evidence of a difference in hemangioma size (as a measure of resolution) when measured by the proportion of patients with a clinician-assessed reduction of 50% or greater (RR 1.13, 95% CI 0.64 to 1.97; 1 study; 26 participants; low-quality evidence).⁵ Although there were more short- or long-term general adverse effects (such as severe diarrhea, lethargy, and loss of appetite) in the oral propranolol group, there was no evidence of a difference between groups (RR 7.00, 95% CI 0.40 to 123.35; 1 study; 26 participants; very low-quality evidence).⁵ This comparison did not measure clearance.⁵ There was no evidence of a difference between oral propranolol and topical timolol maleate in their ability to generate a 50% or greater reduction in infantile hemangioma size, based on low-quality evidence.⁵ Very low-quality evidence about adverse events made it difficult to draw conclusions about the comparative safety of oral propranolol versus topical timolol in managing infantile hemangioma.⁵

In summary, there is limited evidence for the treatment of infantile hemangiomas as a large number of interventions and outcomes have not been assessed in RCTs.⁵ Key results from the 28 RCTs indicate that in the management of infantile hemangioma in children, oral propranolol and topical timolol maleate are more beneficial than placebo in terms of clearance or other measures of resolution, or both, without an increase in harms.⁵ No evidence of a difference between oral propranolol and topical timolol maleate was identified with regard to reducing hemangioma size, but it is uncertain if there is a difference in safety.⁵ However, these results are based on moderate- to very low-quality evidence.⁵

After review, 15 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).³⁵⁻⁵⁰

New Guidelines

High Quality Guidelines:

International Society of Hypertension

The 2020 IHS guideline was developed to provide recommendations for the management of hypertension in adults, aged 18 years and older.⁶ Despite several initiatives, the prevalence of raised blood pressure and adverse impact on cardiovascular morbidity and mortality are increasing globally, irrespective of income.⁶ In accordance with most major guidelines, it is recommended that hypertension be diagnosed when a person's SBP in the office or clinic is 140 mmHg or higher and/or their diastolic blood pressure (DBP) is 90 mmHg or higher, following repeated examination.⁶ Beta blockers should be considered when there is a specific indication for their use, such as with heart failure, angina, post-MI, atrial fibrillation, or in hypertensive women planning pregnancy or currently pregnant.⁶ In patients with hypertension and heart failure, renin-angiotensin-system (RAS) blockers, beta-blockers, and MRAs are all effective in improving clinical outcome in patients with established HFrEF, whereas for diuretics, evidence is limited to symptomatic improvement.⁶ Recommended first-line oral pharmacotherapy options in gestational hypertension include methyldopa, labetalol, and nifedipine.⁶ Contraindicated therapies include RAS blockers (e.g., ACEI, ARB, and direct renin inhibitors) because of adverse fetal and neonatal outcomes.⁶

American College of Obstetricians and Gynecologists: Gestational Hypertension and Preeclampsia

A 2020 ACOG Practice Bulletin summary addressed optimal antihypertensive treatment for women with gestational hypertension or preeclampsia.⁷ Antihypertensive treatment should be initiated for severe hypertension (SBP of 160 mm Hg or more or DBP of 110 mm Hg or more, or both) that is confirmed as persistent.⁷ Parenteral antihypertensive therapy may be needed initially for acute control of blood pressure, however, oral medications can be used as expectant management is continued.⁷ Oral labetalol and calcium channel blockers have been commonly used.⁷ One approach is to begin an initial regimen of labetalol at 200 mg orally every 12 hours and increase the dose up to 800 mg orally every 8–12 hours as needed (maximum total 2,400 mg/day).⁷ If the maximum dose is inadequate to achieve the desired blood pressure goal, or the dosage is limited by adverse effect, then short-acting oral nifedipine can be added gradually.⁷

European Society of Cardiology: Management of Chronic Coronary Syndromes

The 2019 ESC guidance for management of chronic coronary syndromes updated 2013 guidance focused on management of stable CAD.⁸ Coronary artery disease is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive.⁸ The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion.⁸ The dynamic nature of the CAD process results in various clinical presentations, which can be categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes.⁸ The most frequently encountered clinical scenarios in patients with suspected or established chronic coronary syndrome are: 1) patients with suspected CAD and stable anginal symptoms or dyspnea; 2) patients with new onset of heart failure or left ventricular dysfunction and suspected CAD; 3) asymptomatic and symptomatic patients with stabilized symptoms less than 1 year after an ACS event, or patients with recent revascularization; 4) asymptomatic and symptomatic patients 1 year or longer after initial diagnosis or revascularization; 5) patients with angina and suspected vasospastic or microvascular disease; and 6) asymptomatic subjects in whom CAD is detected at screening.⁸ All of these scenarios are classified as a chronic coronary syndrome, but involve different risks for future cardiovascular events (e.g. death or MI) and the risk may change over time.⁸

Beta blockers can be combined with dihydropyridine (DHP) CCBs (e.g., long-acting nifedipine or amlodipine) to reduce DHP-induced tachycardia, but with uncertain incremental clinical value.⁸ Caution is warranted when a beta blocker is combined with non-dihydropyridine CCBs (e.g., verapamil or diltiazem) due to

the potential for developing worsening of heart failure, excessive bradycardia, or atrioventricular block.⁸ The ESC recommendation on anti-ischemic drugs in patients with chronic coronary syndrome is as follows:

- First-line treatment is indicated for angina/ischemia relief with beta blockers or non-dihydropyridine CCBs to control heart rate and symptoms (Class I recommendation: evidence that a given treatment is beneficial, useful, and effective. Class A level of evidence: data is derived from multiple RCTs or meta-analyses).⁸

In certain patients with recent MI and those with chronic HFrEF, beta blockers have been associated with a significant reduction in mortality and/or cardiovascular events, but the protective benefit in patients with CAD without prior MI or heart failure is less well established and lacks placebo-controlled trials.⁸ A retrospective analysis of 21,860 matched patients from the REACH (Reduction of Atherothrombosis for Continued Health) Registry showed no reduction in cardiovascular mortality with beta-blockers in patients with either CAD with risk factors only, known prior MI, or known CAD without MI.⁸ In a retrospective national registry of 755,215 patients aged 65 years and older with a history of CAD without prior MI or heart failure with reduced ejection fraction undergoing elective percutaneous coronary intervention (PCI), beta blocker use at discharge was not associated with any reduction in cardiovascular morbidity or mortality at 30-day and 3-year follow-up.⁸ However, in patients with or without previous MI undergoing coronary artery bypass grafting (CABG), beta-blockers were associated with lower risk of long-term mortality and adverse cardiovascular events.⁸ Other observational studies and meta-analyses have questioned the benefit of long-term (greater than 1 year) beta blocker therapy in patients with a previous MI.⁸ This is still a matter for debate, and uncertainties remain on the comparative role of beta blockers and ACEIs/ARBs.⁸

European Society of Cardiology: Treatment of Heart Failure

The aim of the 2021 ESC Guideline is to help health professionals manage people with heart failure according to the best available evidence.⁹ In the updated publication, each phenotype of heart failure, based on LVEF, is addressed separately in terms of diagnosis and management.⁹ The diagnosis of mild HFrEF requires the presence of symptoms or signs of heart failure, and a mildly reduced ejection fraction (41 to 49%).⁹ There is a substantial overlap of clinical characteristics, risk factors, patterns of cardiac remodeling, and outcomes among the LVEF categories in heart failure.⁹ Patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF, in that they are more commonly men, younger, and are more likely to have CAD (50 to 60% prevalence), and less likely to have AF and non-cardiac comorbidities.⁹ However, ambulatory patients with HFmrEF have a lower mortality than those with HFrEF, more akin to those with HFpEF.⁹ There is no specific trial of beta-blockade in HFmrEF.⁹ Since many patients with HFmrEF may have another cardiovascular indication for a beta blocker (e.g., atrial fibrillation or angina), treatment with beta blockers may be considered in patients with HFmrEF.⁹

The diagnosis of HFpEF requires objective evidence of cardiac structural, or functional abnormalities as well as elevated plasma natriuretic peptide concentrations consistent with the presence of LV diastolic dysfunction and raised LV filling pressures.⁹ A diastolic stress test is recommended when these markers are equivocal.⁹ Heart failure with preserved ejection fraction of 50% or more differs from HFrEF and HFmrEF in that HFpEF patients are older and more often female.⁹ Atrial fibrillation, chronic kidney failure, and non-cardiovascular comorbidities are more common in patients with HFpEF than in those with HFrEF.⁹ To date, no treatment has been shown to reduce mortality and morbidity in patients with HFpEF.⁹ Despite the lack of evidence for specific disease-modifying therapies in HFpEF, as the vast majority of HFpEF patients have underlying hypertension and/or CAD, many are already treated with ACE-I/ARB, beta-blockers, or MRAs.⁹

There are 3 major goals of treatment for patients with HFrEF: 1) reduction in mortality, 2) prevention of recurrent hospitalizations due to worsening HF, and 3) improvement in clinical status, functional capacity, and quality of life.⁹ The triad of an ACEI or ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for patients with HFrEF, unless the drugs are contraindicated or not tolerated.⁹ The dose should be titrated up to the doses used in the clinical trials (or

to maximally tolerated doses if that is not possible).⁹ **Table 2** provides specific, evidence-based, beta blocker dose recommendations.⁹ Specific beta blockers (**Table 2**) have been shown to reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACEI and diuretic.⁹ They also improve heart failure symptoms.⁹ There is consensus that ACEI and beta blockers can be started together as soon as the diagnosis of symptomatic HFrEF is established.⁹ There is no evidence favoring the initiation of a beta blocker before an ACEI and vice versa.⁹ Beta blockers should be initiated in clinically stable, euvolemic, patients at a low dose and gradually up titrated to the maximum tolerated dose.⁹ In patients admitted with acute heart failure, beta blockers should be cautiously initiated in the hospital, once the patient is hemodynamically stabilized.⁹

Table 2. Evidence-based doses of disease-modifying beta-blockers in patients with heart failure with reduced ejection fraction⁹

Beta blocker	Starting Dose	Target Dose
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily*
Metoprolol Succinate (extended-release)	12.5 to 25 mg once daily	200 mg once daily

*A maximum dose of 50 mg twice daily can be administered to patients weighing over 85 kg

Specific recommendations regarding the use of beta blockers to treat different stages of heart failure and the quality of evidence supporting the recommendation are:

- A beta blocker may be considered in patients with mild HFrEF to reduce the risk of heart failure hospitalization and death. (Class 2B recommendation; efficacy is less well established by evidence. Class C level of evidence: consensus of opinion of experts or small studies, retrospective studies, and registries).⁹
- A beta blocker is recommended for patients with stable HFrEF to reduce the risk of heart failure hospitalization and death. (Class I recommendation: evidence that a given treatment is beneficial, useful, and effective. Class A level of evidence: data derived from multiple RCTs or meta-analyses).⁹

Atrial fibrillations and heart failure frequently coexist.⁹ They can cause or exacerbate each other through mechanisms such as structural cardiac remodeling, activation of neurohormonal systems, and rate-related LV impairment.⁹ The proportion of patients with heart failure who develop atrial fibrillation increases with age and heart failure severity.⁹ When atrial fibrillation causes heart failure, the clinical course seems more favorable than with other causes of HF.⁹ In contrast, development of atrial fibrillations in patients with chronic heart failure is associated with worse prognosis, including stroke and increased mortality.⁹ Beta-blockers can be used for rate control in patients with HFrEF or mild HFrEF because of their established safety in these patients.⁹ Recommendations for management of patients with heart failure and atrial fibrillation includes beta blocker therapy. For HFpEF, there is a paucity of evidence to demonstrate efficacy of any agent. There is insufficient evidence in favor of a strategy of rhythm control with antiarrhythmic drugs versus rate control in patients with heart failure and atrial fibrillation.⁹

Recommendation:

- Beta blockers should be considered for short- and long-term rate control in patients with heart failure and atrial fibrillation. (Class 2A recommendation: weight of evidence is on favor of efficacy. Class B level of evidence: data derived from a single RCT or large non-randomized studies).⁹

Canadian Cardiovascular Society/Canadian Heart Rhythm Society: Management of Atrial Fibrillation

The 2020 Canadian Cardiovascular Society(CCS)/Canadian Heart Rhythm Society guideline on management of atrial fibrillation is an update of 2010 guidance.¹⁰ Atrial fibrillation, the most common sustained cardiac arrhythmia, is associated with reduced quality of life, functional status, cardiac performance, and survival.¹⁰ The management of atrial fibrillation is centered on symptomatic improvement, decreasing morbidity outcomes and mortality , and reduction in atrial

fibrillation-related emergency department (ED) visits or hospitalizations.¹⁰ In the setting of recent onset atrial fibrillation, the rate control agent and the formulation chosen will be influenced by clinical circumstance (e.g., the presence of heart failure or hypotension) and patient comorbidities (e.g., known LV dysfunction, reactive airways disease, hypotension, history of MI, or angina).¹⁰ Options include oral or intravenous beta blockers, oral or intravenous non-dihydropyridine CCBs, intravenous digoxin, and intravenous amiodarone (recognizing that the latter is also a rhythm control agent).¹⁰ Beta blockers are preferred in patients with acute coronary syndrome who require acute rate control.¹⁰ Intravenous rate control agents might be initially considered in patients who are not hemodynamically stable.¹⁰

Recommendations:

- ◆ Either beta blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for atrial fibrillation rate control in patients without significant LV dysfunction (e.g., patients with an LVEF greater than 40%) (strong recommendation; moderate-quality evidence).¹⁰
- ◆ Beta blockers bisoprolol, carvedilol and metoprolol are preferred for rate control of hemodynamically stable atrial fibrillation in the acute care setting in patients with significant LV dysfunction (e.g., patients with an LVEF 40% or less) (strong recommendation; moderate-quality evidence).¹⁰

Pharmacotherapy for long-term atrial fibrillation rate control revolves around agents with negative dromotropic properties such as beta blockers and non-dihydropyridine CCBs verapamil and diltiazem.¹⁰ The choice of a specific rate-controlling regimen should be based on patient characteristics and the drug's efficacy and side effect profile.¹⁰ In patients without significant LV dysfunction (LVEF less than 40%), beta blockers and non-dihydropyridine CCBs are first-line options.¹⁰ There are no randomized long-term data to support choosing a beta blocker over a non-dihydropyridine CCB. Several retrospective studies of atrial fibrillation patients have shown conflicting results when rates of hospital admission were compared after using beta-blockers versus CCBs: one showed no difference whereas another showed that use of CCBs was associated with a higher rate of hospitalization compared with beta blocker use.¹⁰ Beta blockers might be more effective long-term at slowing ventricular rates at rest and during exercise; however, their use is associated with a higher risk of adverse effects like fatigue and exercise intolerance.¹⁰ Moreover, there is emerging evidence suggesting that CCBs might have favorable dose-response characteristics for atrial fibrillation rate control versus beta blockers, such that they might be preferred in patients with a preserved LVEF and without another indication for a beta blocker.¹⁰ Specific patient characteristics might favor the use of one pharmacological class (e.g., non-dihydropyridine CCBs with hypertension or reactive airway disease versus beta-blockers with CAD).¹⁰ Caution should be used when beta-blockers are used with verapamil or diltiazem.¹⁰

Recommendations:

- ◆ Beta-blockers or non-dihydropyridine CCBs (diltiazem or verapamil) are first-line agents for rate control of atrial fibrillation in patients without significant LV dysfunction (strong recommendation; moderate-quality evidence).¹⁰
- ◆ Evidence-based beta blockers (bisoprolol, carvedilol, metoprolol) are first-line agents for rate control of atrial fibrillation in patients with significant LV dysfunction (strong recommendation; moderate-quality evidence).¹⁰

British Society Of Gastroenterology/British Association For The Study Of The Liver: Management Of Ascites In Cirrhosis¹¹

In 2021 the British Society of Gastroenterology in collaboration with British Association for the Study of the Liver updated 2007 guidance on the management of ascites in cirrhosis.¹¹ In recent years, there has been increasing recognition that the benefits of non-selective beta blockers in patients with cirrhosis may not be exclusively explained by the reduction in portal pressure.¹¹ Non-selective beta blockers reduce markers of intestinal permeability, bacterial translocation, systemic inflammation and the incidence of spontaneous bacterial peritonitis independently of hemodynamic response, suggesting a direct effect, potentially via intestinal transit time or on the bowel mucosal integrity.¹¹ Given the mounting evidence that bacterial translocation and the systemic inflammatory response contribute to the downward spiral of circulatory dysfunction in cirrhosis, it follows that non-selective beta blockers may also reduce non-bleeding related mortality.¹¹ Until randomized high-quality data are available, the current evidence supports the use of non-selective beta blockers when indicated in patients with refractory ascites, unless alternative markers of circulatory failure, such as hypotension or reduced glomerular filtration rate, are present.¹¹

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Recommendations:

- ◆ Refractory ascites should not be viewed as a contraindication to non-selective beta blockers (strong recommendation; moderate-quality evidence).¹¹
- ◆ Patients with refractory ascites who are taking non-selective beta blockers should be monitored closely, and dose reduction or discontinuation may be appropriate in those who develop hypotension or acute/progressive renal dysfunction (strong recommendation; moderate-quality evidence).¹¹

American Academy of Pediatrics: Management of Infantile Hemangiomas

In 2019, the AAP published a clinical practice guideline on the management of infantile hemangioma.¹² Systemic therapy with corticosteroids was considered the standard of care for several decades before being replaced by oral propranolol.¹² Oral propranolol is now recommended over oral corticosteroids to avoid the adverse effects associated with corticosteroid therapy.¹² Caution is advised for the use of propranolol in infants less than 5 weeks of age or postconceptional age of less than 48 weeks.¹² As other beta blockers, use of propranolol should be avoided in patients with cardiogenic shock or heart failure, sinus bradycardia, heart block greater than first degree, presence or risk of coarctation of the aorta and cerebrovascular anomalies, or asthma.¹² Treatment of infantile angioma with topical application of ophthalmic timolol maleate 0.5% gel has shown modest benefit in clearing small (less than 1 mm thick), superficial lesions (expected clearance 62%).¹² The adverse effects associated with topical timolol are low, but include a possible risk of local irritation, sleep disturbance, cold extremities, bronchospasm, and bradycardia.¹² Additional caution is advised in preterm infants and those without intact skin (i.e., ulceration).¹²

The pharmacotherapy recommendations are as follows:

- ◆ Use propranolol as the first-line agent for infantile hemangioma requiring systemic treatment (strong recommendation; high-quality evidence).¹²
- ◆ Dose propranolol between 2 and 3 mg/kg per day unless there are comorbidities or adverse effects (e.g., sleep disturbance) that necessitate a lower dose (strong recommendation; moderate-quality evidence).¹²
- ◆ May prescribe oral prednisolone or prednisone to treat infantile hemangioma if there are contraindications or inadequate response to oral propranolol (moderate recommendation; moderate-quality evidence).¹²
- ◆ May prescribe topical timolol maleate as a therapy for thin and/or superficial infantile hemangioma (moderate recommendation; moderate-quality evidence).¹²

After review, 2 guidelines were excluded due to poor quality.^{51,52}

New Formulations or Indications:

A new dosage form of metoprolol succinate received Food and Drug Administration (FDA) approval on 1/26/18. Metoprolol succinate extended-release capsules (KAPSPARGO SPRINKLE) are formulated for once daily administration.⁵³ It is approved for treatment of hypertension, angina pectoris, and heart failure. The capsule should be swallowed whole, but for patient unable to swallow an intact capsule, alternative administration options are available.⁵³ The capsule can be opened and the contents sprinkled over soft food.⁵³ The contents of the capsules should be swallowed along with a small amount (teaspoonful) of soft food such as applesauce, pudding or yogurt.⁵³ The drug/food mixture should be swallowed within 60 minutes and not stored for future use.⁵³ The contents of the capsule can also be diluted in 15 mL of water and administered via a nasogastric tube.⁵³

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts⁵⁴

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Metoprolol Succinate	TOPROL-XL	1/12/2022	Boxed Warning Warnings and Precautions	New section on bradycardia added: <i>Bradycardia, including sinus pause, heart block, and cardiac arrest have occurred with the use of TOPROL-XL. Patients with first-degree atrioventricular block, sinus node dysfunction, conduction disorders (including Wolff- Parkinson-White) or on concomitant drugs that cause bradycardia, may be at increased risk. Monitor heart rate in patients receiving TOPROL-XL. If severe bradycardia develops, reduce or stop TOPROL-XL.</i>
Propranolol	HEMANGEOL	6/22/2021	Warnings and Precautions	Hypoglycemia section revised (additions are underlined) HEMANGEOL prevents the response of endogenous catecholamines to correct hypoglycemia and masks the adrenergic warning signs of hypoglycemia, particularly tachycardia, palpitations and sweating. HEMANGEOL can cause hypoglycemia, <u>at any time during treatment.</u> <u>Risk is increased during a fasting period (e.g., poor oral food intake, infection, vomiting) or when glucose demands are increased (e.g., cold, stress, infections).</u> Withhold the dose under these conditions. Hypoglycemia may present in the form of seizures, lethargy, or coma. <u>Discontinue HEMANGEOL if hypoglycemia develops and treat appropriately.</u>
Propranolol	HEMANGEOL	4/2/2020	Adverse Reactions	Skin and subcutaneous tissues disorders: dermatitis psoriasiform added to this section.

Randomized Controlled Trials:

A total of 797 citations were manually reviewed from the initial literature search. After further review, 794 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Kim, SG et al ⁵⁵ OL, MC, RCT Duration: 6 weeks	1. Carvedilol 6.25 mg to 12.5 mg po daily dose (mean dose = 11.25 mg)* Vs. 2. Propranolol 40 to 320 po daily dose (mean dose = 153 mg)* *Titrated to HR decreased by 25% or 55 beats/min and SBP > 90 mm Hg	Adults aged 20-70 yo with cirrhosis and esophageal varices with baseline HVPG > 12 mm Hg N=110	Decrease in mean HVPG by 20% compared with baseline or less than 12 mm Hg at 6 weeks	Decrease in mean HVPG at 6 weeks 1. -3.5 ± 4.8 mm Hg 2. -2.0 ± 5.5 mm Hg Difference: -1.5 mm Hg CI NR P=0.163	Open label study design Small population size
Kim, HG et al ⁵⁶ NI, RCT Duration: 16 weeks	1. Propranolol 2 mg/kg/day po (n=17) Vs. 2. Prednisolone 2 mg/kg/day po (n=17)	Children aged 0 to 9 mo (mean age: 3.3 mo) with and IH, IH-related organ dysfunction and IH-related aesthetic issue N=34	Hemangioma volume change from baseline to 16 weeks NI margin: -20%	Hemangioma Volume Reduction at 16 weeks 1. 55.87% 2. 46.52% Difference: 9.35 CI NR P=0.27	NI study design Small population size
Kalambokis GN, et al. ⁵⁷ SC, RCT	1. Carvedilol 12.5 mg per day (n=58) Vs. 2. Propranolol 75 mg per day (n=32)	Adults 18 to 75 yo with cirrhosis and ascites, treated with propranolol for esophageal variceal bleeding prophylaxis N=96	Primary endpoints: liver-related mortality; and occurrence of new decompensating events (reappearance of ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding) within a 2-year follow-up	Liver-related Death 1. 12% 2. 37.5% P=0.02 CI NR Frequency of Decompensating Events 1. 10.3% 2. 37.5% P=0.002 CI NR	-Small patient population -Selection bias due to strict inclusion criteria and exclusion of patients not responding or intolerant to carvedilol

Abbreviations: CI = confidence interval; HR = heart rate; HVPG = hepatic venous pressure gradient; IH = infantile hemangioma; kg = kilogram; mg = milligrams; MC = multicenter; mo = months; NI = noninferiority; NR = not reported; PC = placebo controlled; po = oral; RCT = randomized clinical trial; SBP = systolic blood pressure; SC = single center; yo = years old.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
acebutolol HCl	ACEBUTOLOL HCL	ORAL	CAPSULE	Y
atenolol	ATENOLOL	ORAL	TABLET	Y
atenolol	TENORMIN	ORAL	TABLET	Y
carvedilol	CARVEDILOL	ORAL	TABLET	Y
carvedilol	COREG	ORAL	TABLET	Y
labetalol HCl	LABETALOL HCL	ORAL	TABLET	Y
metoprolol succinate	METOPROLOL SUCCINATE	ORAL	TAB ER 24H	Y
metoprolol succinate	TOPROL XL	ORAL	TAB ER 24H	Y
metoprolol tartrate	LOPRESSOR	ORAL	TABLET	Y
metoprolol tartrate	METOPROLOL TARTRATE	ORAL	TABLET	Y
propranolol HCl	PROPRANOLOL HCL	ORAL	TABLET	Y
betaxolol HCl	BETAXOLOL HCL	ORAL	TABLET	N
bisoprolol fumarate	BISOPROLOL FUMARATE	ORAL	TABLET	N
carvedilol phosphate	CARVEDILOL ER	ORAL	CPMP 24HR	N
carvedilol phosphate	COREG CR	ORAL	CPMP 24HR	N
metoprolol succinate	KASPARGO SPRINKLE	ORAL	CAP SPR 24	N
nadolol	CORGARD	ORAL	TABLET	N
nadolol	NADOLOL	ORAL	TABLET	N
nebivolol HCl	BYSTOLIC	ORAL	TABLET	N
nebivolol HCl	NEBIVOLOL HCL	ORAL	TABLET	N
pindolol	PINDOLOL	ORAL	TABLET	N
propranolol HCl	INDERAL XL	ORAL	CAP ER 24H	N
propranolol HCl	INNOPRAN XL	ORAL	CAP ER 24H	N
propranolol HCl	INDERAL LA	ORAL	CAP SA 24H	N
propranolol HCl	PROPRANOLOL HCL ER	ORAL	CAP SA 24H	N
propranolol HCl	HEMANGEOL	ORAL	SOLUTION	N
propranolol HCl	PROPRANOLOL HCL	ORAL	SOLUTION	N
sotalol HCl	SOTYLIZE	ORAL	SOLUTION	N
sotalol HCl	BETAPACE	ORAL	TABLET	N
sotalol HCl	BETAPACE AF	ORAL	TABLET	N
sotalol HCl	SORINE	ORAL	TABLET	N
sotalol HCl	SOTALOL	ORAL	TABLET	N
sotalol HCl	SOTALOL AF	ORAL	TABLET	N
timolol maleate	BLOCADREN	ORAL	TABLET	N
timolol maleate	TIMOLOL MALEATE	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

A Randomized, Multi-Center, Open-Label Study to Evaluate the Efficacy of Carvedilol vs. Propranolol to Reduce Portal Pressure in Patients With Liver Cirrhosis⁵⁵

Objectives: Propranolol has been used as prophylaxis for variceal bleeding in patients with cirrhosis. More recent data suggest that carvedilol may be more effective for reducing the hepatic venous pressure gradient (HVPG) than propranolol. The primary aim of this study was to evaluate the hemodynamic response to carvedilol compared with propranolol.

Methods: A total of 110 patients with a baseline HVPG value >12 mm Hg were allocated randomly to receive either carvedilol or propranolol. The HVPG measurement was repeated after 6 weeks of daily medication. The primary end point was a $\geq 20\%$ fall in HVPG compared with baseline or <12 mm Hg.

Results: The difference in the proportion of responders in the carvedilol (49.1%) vs. propranolol (30.9%) groups did not reach statistical significance in the intention-to-treat analysis ($P=0.08$). However, among patients with a model for end-stage liver disease (MELD) score ≥ 15 , carvedilol resulted in a significantly greater response than that of propranolol (7/12, 58.3% vs. 0/10, 0%; $P=0.005$). Similarly, carvedilol was superior to propranolol in patients with Child-Pugh score ≥ 9 (46.2 vs. 0%; $P=0.046$). The presence of ascites also had a significant influence on the response rate (51.5 vs. 24.2%; $P=0.042$). A MELD score ≥ 15 was the only significant predictor of response among these post hoc groups after adjusting for multiple comparisons ($P=0.005$). Severe adverse events were higher in the carvedilol group although drug-associated adverse events were not different.

Conclusions: Overall, carvedilol offered no clear advantage over propranolol but it may be more effective in advanced cirrhotic patients with a MELD score ≥ 15 in reducing the portal pressure gradient. However, this potential benefit may come with a cost of increased risk of side-effects and outcome data over a longer term is needed to understand the relative risk benefit.

Comparison of Efficacy and Safety Between Propranolol and Steroid for Infantile Hemangioma⁵⁶

Objective: To determine the efficacy and safety of propranolol compared with steroid as a first-line treatment for infantile hemangioma (IH).

Design, Setting, and Participants: This randomized clinical noninferiority trial tested the efficacy and safety of propranolol vs steroid treatment for IH at a single academic hospital. All participants were diagnosed with IH between June 2013 and October 2014, had normal heart function, and had not been previously treated for IH.

Interventions: The participants were randomly assigned to either the propranolol group or the steroid group. In the propranolol group, the patients were admitted, observed for adverse effects for 3 days after treatment initiation, and then released and treated as outpatients for 16 weeks (2 mg/kg/d). In the steroid group, the patients were seen as outpatients from the beginning and were also treated for 16 weeks (2 mg/kg/d).

Main Outcomes and Measures: The primary efficacy variable was the response to treatment at 16 weeks, which was evaluated by the hemangioma volume using magnetic resonance imaging before and at 16 weeks after treatment initiation. While comparing the effect of medication between the groups, we monitored the adverse effects of both drugs.

Results: A total of 34 patients (15 boys, 19 girls; mean age, 3.3 months; range, 0.3-8.2 months) were randomized to receive either propranolol or steroid treatment (17 in each treatment group). Guardians for 2 patients in the steroid group withdrew their consent, and 1 patient in the propranolol group did not complete the efficacy test. The intention-to-treat analysis, applying multiple imputations, found the treatment response rate in the propranolol group to be 95.65%, and that of the steroid group was 91.94%. Because the difference in response rate between the groups was 3.71%, propranolol was considered noninferior. We found that there was no difference between the groups in safety outcomes.

Conclusions and Relevance: Our trial demonstrated that propranolol was not inferior to steroid with respect to therapeutic effects in IH.

Conversion of Propranolol to Carvedilol Improves Renal Perfusion and Outcome in Patients With Cirrhosis and Ascites⁵⁷

Background: In recent years, concerns have been raised on the potential adverse effects of nonselective beta-blockers, and particularly carvedilol, on renal perfusion and survival in decompensated cirrhosis with ascites. We investigated the long-term impact of converting propranolol to carvedilol on systemic hemodynamics and renal function, and on the outcome of patients with stable cirrhosis and grade II/III nonrefractory ascites.

Patients and Methods: Ninety-six patients treated with propranolol for esophageal varices' bleeding prophylaxis were prospectively evaluated. These patients were randomized in a 2:1 ratio to switch to carvedilol at 12.5 mg/d (CARVE group; n=64) or continue propranolol (PROPRA group; n=32). Systemic vascular resistance, vasoactive factors, glomerular filtration rate, and renal blood flow were evaluated at baseline before switching to carvedilol and after 6 and 12 months. Further decompensation and survival were evaluated at 2 years.

Results: During a 12-month follow-up, carvedilol induced an ongoing improvement of systemic vascular resistance (1372 ± 34 vs. 1254 ± 33 dynes/cm⁵; $P=0.02$) along with significant decreases in plasma renin activity (4.05 ± 0.66 vs. 6.57 ± 0.98 ng/mL/h; $P=0.01$) and serum noradrenaline (76.7 ± 8.2 vs. 101.9 ± 10.5 pg/mL; $P=0.03$) and significant improvement of glomerular filtration rate (87.3 ± 2.7 vs. 78.7 ± 2.3 mL/min; $P=0.03$) and renal blood flow (703 ± 17 vs. 631 ± 12 mL/min; $P=0.03$); no significant effects were noted in the PROPRA group. The 2-year occurrence of further decompensation was significantly lower in the CARVE group than in the PROPRA group (10.5% vs. 35.9%; $P=0.003$); survival at 2 years was significantly higher in the CARVE group (86% vs. 64.1%; $P=0.01$, respectively).

Conclusion: Carvedilol at the dose of 12.5 mg/d should be the nonselective beta-blocker treatment of choice in patients with cirrhosis and nonrefractory ascites, as it improves renal perfusion and outcome.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1996 to May Week 1, 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to May 16, 2022

1	exp Acebutolol/	857
2	exp Atenolol/	5258
3	exp Carvedilol/	2813
4	exp Labetalol/	1881
5	exp Metoprolol/	5627
6	exp Betaxolol/	669
7	exp Bisoprolol/	1182
8	exp Nadolol/	822
9	exp Nebivolol/	842
10	exp Pindolol/	3711
11	exp Propranolol/	32757
12	exp Sotalol/	2109
13	Timolol/	3810
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	56140
15	limit 14 to (english language and humans and yr=2015-current) and clinical trial, comparative study, controlled clinical trial, guideline, meta-analysis, practice guideline, randomized clinical trial or systematic review	797

Appendix 4: Key Inclusion Criteria

Population	Adults
Intervention	Oral Beta-blockers
Comparator	Placebo, other antihypertensives
Outcomes	All cause-mortality, cardiovascular mortality, myocardial infarction, or stroke
Timing	1 year
Setting	Outpatient