Hypertension: Which drugs to choose for patients with cardiovascular disease

Recommendations for heart failure, coronary artery disease, and stroke

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Practice recommendations

- Decreasing blood pressure by 5 mm Hg will decrease mortality due to stroke by 14%, attenuate cardiac mortality by 9%, and reduce all-cause mortality by 7% (**A**).
- Patients with heart failure should receive angiotensin-converting enzyme inhibitors if they are clinically tolerated (**A**). Beta-blockers are also recommended (**A**). Although aldosterone antagonists are appropriate for use in patients with heart failure (**A**), we recommend they are taken under the care of a cardiologist to minimize complications and to insure that a complete heart failure plan is in place (**C**).
- For coronary artery disease, it is now considered standard of care to add a beta-blocker to all patients post–MI that do not have severe heart block or are in cardiogenic shock (**A**).
- Perindopril plus indapamide should be used in all patients with a history of stroke or transient ischemic attack regardless of blood pressure (**B**).

Hypertension precedes more than 75% of heart failure cases and 50% of heart attacks. In 67% of first-time strokes, blood pressure exceeds 140/90 mm Hg.[1] For those in heart failure or at risk of recurrent myocardial infarction (MI) or stroke, the need to reduce unrecognized or under-treated hypertension is urgent. Thankfully it is possible to select an agent that can lower blood pressure—the most important immediate goal—and confer benefit to the associated cardiovascular disorder.

Given the number of agents used for both hypertension and other cardiovascular conditions, we sought in this study to evaluate which drug classes would best achieve blood pressure treatment goals and reduce morbidity and mortality for patients with cardiac disease. In this article, you will find practical recommendations for drug selection and appropriate regimens.

Even small blood pressure reductions yield big benefits for comorbidities

Using the population of the National Health and Nutrition Examination Survey I Epidemiologic Follow Up Study, Ogden and colleagues[2] found that the benefit of treating high blood pressure over a decade depended on lowering systolic blood pressure and on treating other relevant cardio-

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TABLE

Drugs of choice for hypertension and various comorbidities

TREATMENT RECOMMENDATIONS BASED ON STUDIES/GUIDELINES	SOR
Congestive Heart Failure	
ACE inhibitor should be used in patients with heart failure unless a contraindication exists[8,9,11,12]	A
Beta-blockers should be used in patients with heart failure unless a contraindication exists[11–15]	A
ARB should be used in heart failure if patient is intolerant to ACE inhibitor[12]	A
Aldosterone antagonists should be used in patients with severe heart failure unless a contraindication exists[16,17]	A
Aldosterone antagonists should be prescribed in consultation with a cardiologist	C
Coronary Artery Disease	
Beta-blockers should be used in patients post-MI unless a contraindication exists[11,13,18,19]	A
CCB should be used in patients with stable coronary artery disease unless a contraindication exists[11,20]	A
ACE inhibitors should be used in patients with stable coronary artery disease and no left ventricular dysfunction unless a contraindication exists[11,21,22]	A
Stroke	
ACE inhibitor and indapamide should be used in patients with a TIA or stroke unless a contraindication exists[11,23]	B

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; MI, myocardial infarction; SOR, strength of recommendation; TIA, transient ischemic attack

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A small reduction in blood pressure will yield a very significant reduction in risk from cardiovascular disease

vascular comorbidities. Specifically, the number needed to treat (NNT) and prevent a death was directly related to the risk stratification of patients and their initial blood pressure (**TABLE W1**, available at www.jfponline.com) (LOE: **1**).

In another provocative trial, the Swedish Trial in Old Patients with Hypertension-2 Study (STOP Hypertension-2)[3] evaluated the use of beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or calcium channel blockers. Results of this trial showed that an overall reduction in cardiovascular events related to the ability of a drug class to lower blood pressure (LOE: **1**).[3]

In addition, a meta-analysis of 29 randomized trials (n=162,341) in the Blood Pressure Lowering Treatment Trialists' Collaboration Trial (BPLTTC)[4] showed that all antihypertensive drug classes significantly reduce blood pressure. This meta-analysis confirmed an overall reduction in cardiovascular events, with perceived risk reduction directly proportional to blood pressure reduction (LOE: **1**). This advantage was consistent irrespective of drug class (beta-blocker, diuretic, ACE inhibitor, calcium-channel blocker, or angiotensin receptor blocker [ARB]), although different drug classes were recognized to have unique benefits specific to individual patient populations.

Should the BP target level be lowered?

Recent evidence suggests that the currently accepted range for *normal* blood pressure may be too high.[5,6]

Lewington and colleagues performed a meta-analysis of 61 prospective studies with more than 1 million participants. Using a "time-dependent" correction for regression dilution, they sorted deaths in each decade of age according to estimated blood pressures at the start of the decade (LOE: **1**).[5] They found that with each decade of life there was a proportional

decline in the risk of cardiovascular deaths when blood pressures were controlled incrementally to levels of 115 mm Hg systolic blood pressure and 75 mm Hg diastolic blood pressure (LOE: **1**).[5] At blood pressures below 115/75 mm Hg, no difference was observed.

In addition, Vasan and collaborators,[6] using the Framingham Heart Study database (n=6859 participants), reported an increase in cardiovascular events with higher baseline levels of blood pressure. When compared with optimal blood pressure levels, those with *high-normal* blood pressure (130–139/85–89 mm Hg) had a risk-factor-adjusted hazard ratio for cardiovascular disease of 2.5 for women and 1.6 for men (LOE: **1**).[6]

The "take-home" message. A small reduction in blood pressure yields a very significant risk reduction. *Decreasing blood pressure by 5 mm Hg will decrease mortality due to stroke by 14%, cardiac mortality by 9%, and all cause mortality by 7%* (LOE: **1**).[7] These data suggest that aggressive intervention to affect small changes might affect large differences in morbidity and mortality.

Antihypertensive drugs in heart failure

Angiotensin-converting enzyme inhibitors

Give all patients with heart failure an ACE inhibitor, if clinically tolerated (SOR: **A**). Although blood pressure control is very important to treat the physiology and neurohormonal basis of heart failure, the primary reason to use ACE inhibitors (as well as other medications) is to provide a disease modifying intervention and treat blood pressure when it is elevated. Different disease conditions require different doses to achieve the desired goal. With heart failure, the dose of an ACE inhibitor is given twice daily at typically 2 to 3 times the dose of that used for hypertension.

The evidence. In 1991, the Studies of Left Ventricular Dysfunction (SOLVD) trial[8] demonstrated a 26% risk reduction for death or hospitalization due to heart failure (95% confidence interval [CI], 18–34) for those treated with the ACE inhibitor enalapril (Vasotec) (LOE: **1**). The following year, the Survival and Ventricular Enlargement (SAVE)[9] trial demonstrated a risk reduction of 19% for patients with a reduced ejection fraction after myocardial infarction (MI) when the ACE inhibitor captopril (Capoten) was used (LOE: **1**).

The calculated NNT with an ACE inhibitor to save 1 life over 1 year is 43.[10] (See **TABLE W2**, at www.jfponline.com, for a summary of clinical trials and levels of evidence.) The **TABLE** in this article summarizes treatment recommendations based on these studies.[8–23]

Beta-blockers

Give a beta-blocker, if tolerated, to patients in heart failure (SOR: **A**). Dosing has been determined by clinical trial data. In general, in order to significantly impact morbidity and mortality in congestive heart failure, the patient needs to reach a dose of 150 mg of metoprolol XL a day or 6.25 mg to 12.5 mg of carvedilol given twice daily. Ideal doses are greater than 200 mg/d of metoprolol XL or 25 mg twice daily of carvedilol.

The evidence. The Cardiac Insufficiency Bisoprolol Study (CIBIS),[24] published in 1994, was a randomized, placebo-controlled, double-blind trial designed to test the efficacy of beta-blockade in the treatment of heart failure (LOE: **1**). Although no difference in mortality was demonstrated between intervention and control groups, the intervention group showed improved functional status.

The Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN)[13] trial (LOE: **1**) evaluated patients with left ventricular dysfunction or heart failure after an MI, while the Carvedilol Prospective Randomized Cumulative Survey (COPERNICUS)[14] group (LOE: **1**) enrolled only patients with severe heart failure (ejection fraction <25%, NYHA class III and IV). These

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Patients with heart failure should take an ACE inhibitor, typically at doses 2 to 3 times that used for hypertension

Taking JNC-7 to heart

Hypertension specialists debate about how to approach the hypertensive patient. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Management of High Blood Pressure (JNC-7) guidelines[11] call for defined goals in lowering blood pressure and a stepwise selection of drugs based on comorbidities.

Some leading hypertension experts say this is too formulaic. Dr Michael Alderman, Professor in the Department of Medicine and Epidemiology and Population Health at the Albert Einstein School of Medicine, argues "we have to get over the limitation of the straightjacket of numbers to define our actions."[25] He further asserts that "our willingness to drive blood pressure down has to be modulated by the risk the patient has and the price one has to pay to lower it. A 30% reduction in risk does not mean much if your risk is low, but if your risk is high it means a lot."[25] As such, Dr Alderman argues we should base treatment decisions on "total risk" and not the level of blood pressure. Other leaders in the field such as Mathew Weir, MD, director of the Division of Nephrology, University of Maryland, and Richard Devreaux, MD, Professor of Medicine, Division of Cardiology, Cornell University Medical Center, agree with this more individualized approach.[25]

But understanding the basic formula is what helps us innovate. In general, we agree that individualizing patient care is the ideal, and that some patients may not tolerate "recommended" treatment. However, it is not possible for physicians to individualize care (a highly complex undertaking) when they still lack understanding at the basic level of care. With the poor treatment of hypertension in the US, we believe that guidelines such as JNC-7 are essential to improving blood pressure control.

Hyman and Pavlik[26] demonstrated that physician factors, especially lack of awareness of hypertension treatment recommendations, correlate with poor hypertension treatment. In their 2001 study that included 1200 primary care physicians, 41% of physicians were not familiar with or had not heard of the recommendations. This finding was not trivial. The importance of familiarity with JNC-7 guidelines was demonstrated when statistical analysis revealed that a working knowledge of these guidelines significantly increased adherence with published recommendations (including blood pressure control). As such, it would appear that not following the guidelines has less to do with disagreements over treatment options and more to do with understanding the value of the guidelines to basic management.

studies demonstrated an overall decrease in cardiovascular morbidity and mortality, as well as all-cause mortality for patients with heart failure receiving the nonspecific beta-blocker carvedilol (Coreg) (receptor blockade at β_1, β_2, α_1). CAPRICORN produced an overall risk reduction in mortality of 2% to 3% at 1 year, resulting in the same NNT (43) over 1 year as ACE inhibitors.[13] This is the only beta-blocker tested after infarction to demonstrate a mortality difference for patients with heart failure or decreased left ventricular dysfunction (ejection fraction <40%).

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)[15] concluded that the addition of extended-release metoprolol (Lopressor, a β_1-adrenergic receptor blocker) for patients with heart failure demonstrated a survival benefit when compared with patients not receiving a beta-blocker (LOE: **1**). One of the essential elements of this trial was the ability to achieve a dose of 200 mg of metoprolol a day. Frequently in clinical practice low-dose or even homeopathic doses are used with few data to support such use.

The Carvedilol or Metoprolol European Trial (COMET)[27] of patients with heart failure suggested that nonselective neurohumoral (β and α) blockade may increase the benefit in comparison with selective β_1-blockade (LOE: **1**). There has been significant debate regarding the dose and the formulation of the drugs in COMET, but we advocate using doses and drug formulations that were specifically in the large prospective randomized trials (CIBIS II, the carvedilol trials, and MERIT-HF).

Angiotensin receptor blockers

Prescribe an ARB only when a patient cannot tolerate an ACE inhibitor secondary to cough or hyperkalemia.[12] As these are generally used after or as an adjunct to ACE inhibitors, the usual dose is similar to that for blood pressure dosed twice daily. If patients do not tolerate ACE inhibitors, theses doses may also be higher than those

used for blood pressure response alone.

The evidence. The Losartan Heart Failure Survival Study (ELITE II)[28] demonstrated the benefit of the ARB losartan (Cozaar) in the treatment of heart failure, but not superiority over previously used ACE inhibitors (LOE: **1**). In addition, there was no difference in renal insufficiency with one drug class compared with another. Researchers concluded that ARBs should be used only for patients intolerant to ACE inhibitors.

The Valsartan Heart Failure Trial Investigators Study (Val-HeFT)[29] randomized 5010 patients to receive valsartan (Diovan) or placebo combined with standard therapy (ACE inhibitors and beta-blockers) (LOE: **1**). The ARB group demonstrated a 13.2% greater reduction than placebo in the *combined* endpoint of morbidity and mortality (as defined by incidence of cardiac arrest and resuscitation, hospitalization for heat failure, or administration of intravenous inotropes or vasodilators for a minimum of 4 hours). However, a post-study review[29] of patients who received the ARB, ACE inhibitor, and beta-blocker combination showed increased mortality.

In 2004, the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity trial (CHARM)[30] found that when the ARB candesartan (Atacand) was added to standard therapy (ACE inhibitor, beta-blockers, aldosterone antagonist) there was a 33% reduction in all-cause mortality, similar to that found with beta-blockers and ACE inhibitors) (LOE: **1**). In addition, the CHARM group found no increased risk when candesartan was combined with other treatments; it concluded that ARBs could be added to regimens for all patients with heart failure unless a contraindication exists.

The American College of Cardiology/American Heart Association guidelines prefer ACE inhibitors over ARBs, and recommend ARBs be used when an ACE inhibitor is not tolerated or if there are other contraindications. A low level of evidence (**2b**) suggests that an ARB may be added to conventional medical therapy with an increased risk of renal insufficiency and hyperkalemia (SOR: **A**).[12]

Potassium-sparing diuretics

Aldosterone antagonists are appropriate for patients with heart failure (SOR: **A**), though we recommend working in conjunction with a cardiologist to minimize complications and to insure that a complete heart failure plan is in place (SOR: **C**). Spirinolactone (Aldactone, Aldactazide) is used for physiologic purposes (as a neurohormonal regulator) and is not used for blood pressure control. Most heart failure specialists begin with a dose of 12.5 mg/d and advance to doses utilized in the clinical trials (25–50 mg/d).

The evidence. Potassium-sparing diuretics lower mortality among heart failure patients. Spironolactone works in part by reducing aldosterone levels and increasing serum potassium.

In the Randomized Aldactone Evaluation Study (RALES),[16] patients with severe heart failure (ejection fraction <35%) on standard medical therapy were randomized to receive spironolactone or placebo (LOE: **1**). The spironolactone group exhibited a 30% reduction in mortality compared with conventional medical therapy, and the study was ended early at 24 months.

In the Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[17] an overall reduction in death of 8%, a decrease of sudden cardiac death by >20% (relative risk reduction), as well as an overall reduction of hospitalization for heart failure of 15% occurred in the eplerenone (Inspra) group (LOE: **1**) (NNT to save 1 life in 1 year=50).

It is worth noting that the doses used in these studies were devised to alter neurohumoral regulation, and are not to be used as significant diuretics. To date, no comparative study between spironolactone and eplerenone has been undertaken.

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Potassium-sparing diuretics lower mortality among heart failure patients; make a plan with a cardiologist to help minimize complications

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Stable patients without lowered left ventricular function can take an ACE inhibitor or calcium channel blocker in addition to a beta-blocker

Coronary artery disease

Beta-blockers

Prescribe a beta-blocker for every post-MI patient without severe heart block or cardiogenic shock (SOR: **A**).

The evidence. The Beta-Blocker Heart Attack Trial (BHAT),[18] sponsored by the National Heart, Lung, and Blood Institute, was designed to evaluate the benefits of the beta-blocker propranolol (Inderal) after MI (completed more than 24 years ago, before modern medical therapy) (LOE: **1**). Total mortality during the average 24-month follow-up period was 7.2% in the propranolol group and 9.8% in the placebo group. The incidence of nonfatal reinfarction was decreased by 15.6% in the treatment group.

A similar trial completed in the early 1980s was The Norwegian Multi-Center Study.[19] This trial, which assessed the efficacy of timolol (Blocadren, Timolide) after MI, demonstrated a 44.6% reduction in sudden cardiac death (LOE: **1**). The study group reached the same conclusion as the BHAT researchers, and recommended that beta-blockers be used following an MI to reduce reinfarction and death.

Angiotensin-converting enzyme inhibitors

Use ACE inhibitors only for stable post-MI patients without decreased left ventricular function.

The evidence. The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial[31] evaluated the benefit of using an ACE inhibitor for patients with stable coronary artery disease and slightly reduced ejection fraction (>40%) (LOE: **1**). There was no statistical difference in the primary endpoint (cardiac-induced death, MI, or need for revascularization) between the treatment group (21.9%) and the placebo group (22.5%).

Contrary to the findings of the PEACE trial, many other studies have shown that ACE inhibitors are beneficial for patients with coronary artery disease. In the Trandolapril Cardiac Evaluation (TRACE) study,[32] patients stabilized after acute MI were randomized to receive the ACE inhibitor trandolapril (Mavik) or placebo on days 3 to 7 following infarction (LOE: **1**). In the treatment group, risk of death from all causes declined 17.6%, risk of death from cardiovascular causes fell 21%, and progression to severe heart failure decreased 27%. These post-MI benefits are also supported by results of the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study (LOE: **1**).[33]

The Heart Outcomes Prevention Evaluation Investigators (HOPE)[21] (LOE: **1**), and the European Trial on Reduction of Cardiac Events with Perindopril in Patients with Coronary Artery disease (EUROPA)[22] (LOE: **1**), demonstrated the benefits of ACE inhibitors in reducing cardiovascular events for patients with or at risk for coronary artery disease, but with normal left ventricular function. The HOPE study showed a significant reduction of events with the ACE inhibitor ramipril (Altace) (NNT=1000 patients over 4 years, resulting in a decrease of 150 events for 75 patients), whereas EUROPA demonstrated the results for the ACE inhibitor perindopril (Aceon) (NNT=50 patients over 4 years to prevent 1 major cardiovascular event).

Calcium channel blockers

Use calcium channel blockers only for stable post-MI patients without decreased left ventricular function or heart failure.

The evidence. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[20] study compared treatment using a calcium channel blocker (amlodipine) and an ACE inhibitor (enalapril) with placebo for normotensive patients with coronary artery disease (LOE: **1**). Amlodipine reduced hospitalization for angina by 42.2%, nonfatal MI by 26%, and stroke or transient ischemic attack by 50.4% (NNT=16). The study group concluded that the use of the ACE inhibitor enalapril showed "directionally similar, but smaller and nonsignificant, treatment effects."[20] There was no reduction in overall mortality.

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■ Stroke

Prescribe the combination of perindopril and indapamide for all patients with a history of stroke or transient ischemic attack, regardless of blood pressure (SOR: **B**).

The evidence. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[23] was designed to evaluate the benefits of the ACE inhibitor perindopril (with the addition of indapamide at the physician's discretion) for patients with or without hypertension who have had a transient ischemic attack or stroke (LOE: **1**). Perindopril plus indapamide reduced risk of stroke by 43%, but treatment with a single agent showed risk reduction.

Search strategy

To see which drug classes are most often recommended in the treatment of hypertension based on underlying cardiovascular disease, we performed an initial Medline search using the key words *hypertension* and *cardiovascular disease*. This was supplemented with a search of the archives of the journals *Circulation, Hypertension, Stroke,* and the authors' personal references.

All studies were evaluated using the Strength of Recommendation Taxonomy.[34] Strength of recommendation (SOR) evaluates a study based on patient (not disease) oriented outcomes, and level of evidence (LOE) is based on key outcomes as well as the methodology of the study.

FAST TRACK

Perindopril and indapamide reduce risk of stroke by 43% in patients who have had a stroke or transient ischemic attack

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