



Insight

HEART

Vol: 11 No:3 ; 2015



SQUARE
PHARMACEUTICALS LTD.
BANGLADESH

Treatment of Hypertension in Patients With CAD, Stable Angina and ACS

1. Management of Hypertension in Patients With CAD and Stable Angina

- 1.1. Pharmacological Therapy
 - 1.1.1. β -Blockers
 - 1.1.2. Calcium Channel Blockers
 - 1.1.3. ACE Inhibitors
 - 1.1.4. Angiotensin Receptor Blockers
 - 1.1.5. Diuretics
 - 1.1.6. Nitrates
- 1.2. Recommendations

2. Management of Hypertension in Patients With ACS

- 2.1. Prevalence and Impact on Prognosis
- 2.2. General Principles of BP Management in the Patient With ACS
- 2.3. Specific Antihypertensive Agents in ACS
 - 2.3.1. Nitroglycerin
 - 2.3.2. β -Blockers
 - 2.3.3. Calcium Channel Blockers
 - 2.3.4. ACE Inhibitors
 - 2.3.5. Angiotensin Receptor Blockers
 - 2.3.6. Aldosterone Antagonists
 - 2.3.7. Diuretics
- 2.4. Safety of Anticoagulation in Patients With Uncontrolled Hypertension
- 2.5. Conclusions
- 2.6. Recommendations

Cardiology News



Treatment of Hypertension in Patients With CAD, Stable Angina and ACS

1. Management of Hypertension in Patients With CAD and Stable Angina

The management of hypertension in patients with chronic CAD and chronic stable angina is directed toward the prevention of death, MI, and stroke; a reduction in the frequency and duration of myocardial ischemia; and the amelioration of symptoms. Lifestyle changes and the adoption of a heart healthy approach are critical, with the usual attention to diet, sodium intake, moderation of alcohol intake, regular exercise, weight loss, smoking cessation, glycemic control, lipid management, and antiplatelet therapy. Recognition and treatment of hypothyroidism and obstructive sleep apnea are important adjuncts in at-risk patients. Pharmacological management is inevitably required.

A reasonable BP target for hypertensive patients with demonstrated CAD is $<140/90$ mmHg. A lower target BP ($<130/80$ mmHg) may be appropriate in some individuals with CAD or those with previous MI, stroke or transient ischemic attack, or CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm).

1.1. Pharmacological Therapy

1.1.1. β -Blockers

β -Blockers are the drugs of first choice for the treatment of hypertension in patients with CAD that causes angina. They alleviate ischemia and angina primarily as a function of their negative inotropic and chronotropic actions. The decreased heart rate increases diastolic filling time for coronary perfusion. β -Blockers also inhibit renin release from the juxtaglomerular apparatus. Cardioselective (β_1) agents without intrinsic sympathomimetic activity are used most frequently. Relative contraindications to their use include significant sinus or atrioventricular node dysfunction, hypotension, decompensated HF, and severe bronchospastic lung disease.

PAD is rarely made symptomatically worse by the use of these agents, and mild bronchospas-

tic disease is not an absolute contraindication. Caution is needed when brittle diabetic patients with a history of hypoglycemic events are treated because β -blockers may mask the symptoms of hypoglycemia.

Recently, there has been considerable controversy concerning the appropriateness of using β -blockers as first-line therapy in hypertension in those patients who do not have a compelling indication; however, their use in patients with angina, prior MI, or HF has a solid basis of positive data. β -Blockers should be prescribed as initial therapy for the relief of symptoms in patients with stable angina. β -Blockers may be considered as long-term therapy for all other patients with coronary or other vascular disease. Recent ACC Foundation/AHA guidelines have recommended β -blocker therapy in patients with normal LV function after MI or ACS (Class I; Level of Evidence B), specifically carvedilol, metoprolol succinate, or bisoprolol, in all patients with LV systolic dysfunction (ejection fraction $\leq 40\%$) or with HF or prior MI unless contraindicated (Class I; Level of Evidence A). β -Blockers should be started and continued for 3 years in all patients with normal LV function after MI or ACS (Class I; Level of Evidence B).

1.1.2. Calcium Channel Blockers

As a class, CCBs reduce myocardial oxygen demand by decreasing peripheral vascular resistance and lowering BP and increase myocardial oxygen supply by coronary vasodilation. The nondihydropyridine agents diltiazem and verapamil also decrease the sinus node discharge rate and slow atrioventricular nodal conduction.

CCBs or long-acting nitrates should be prescribed for the relief of symptoms when β -blockers are contraindicated or cause unacceptable side effects in patients with stable angina (Class IIa; Level of Evidence B). CCBs or long-acting nitrates in combination with β -blockers should be prescribed for the relief of symptoms when initial therapy with β -blockers is unsuccessful in patients with stable angina (Class IIa; Level of Evidence B). CCBs are



added to, or substituted for, β -blockers when BP remains elevated, when angina persists, or when drug side effects or contraindications mandate. Long-acting dihydropyridine agents are preferred over nondihydropyridines (diltiazem or verapamil) for use in combination with β -blockers to avoid excessive bradycardia or heart block. Diltiazem or verapamil should not be used in patients with HF or LV systolic dysfunction, and short-acting nifedipine should be avoided because it causes reflex sympathetic activation and worsening myocardial ischemia.

Although CCBs are useful in the management of hypertension in patients with stable angina, there is no consensus about their role in preventing cardiovascular events in patients with established CAD. The INVEST investigators randomized >22,000 hypertensive patients with chronic CAD to the nondihydropyridine CCB verapamil or the β -blocker atenolol. By 24 months, the ACE inhibitor trandolapril had to be added in 63% of verapamil patients and 52% of atenolol patients, and hydrochlorothiazide was added in 44% of verapamil and 60% of atenolol patients. There was no difference between the groups in the composite end point of death, MI, or stroke over a mean follow-up of 2.7 years. More than 50% of patients in ALLHAT had a history or signs of atherosclerotic vascular disease, and there was no significant difference in the incidence of coronary end points among patients allocated a thiazide-type diuretic, a long-acting dihydropyridine CCB, or an ACE inhibitor. CAMELOT compared amlodipine or enalapril with placebo in normotensive patients with CAD, \approx 60% of whom had a history of hypertension. Although the BP reduction was similar in the 2 active treatment groups, adverse cardiovascular events occurred less frequently in the amlodipine group than in the enalapril group. An intravascular ultrasound substudy of CAMELOT showed progression of atherosclerosis in the placebo group, a trend toward progression in the enalapril group, and no progression in the amlodipine group.

The VALUE trial randomized 15,245 hypertensive patients at high risk of cardiac events to valsartan or amlodipine. Forty-six percent of patients in both groups had CAD. Mean follow-up was 4.2 years. No difference between groups was observed in the primary composite end point of cardiac morbidity and mortality. The risk of MI was lower in the amlodipine group, whereas the risk of new-onset diabetes mellitus was lower in the valsartan group. Of note, amlodipine was significantly more effective in reducing BP, especially over the first year of the trial. There was also a strong trend for an excess risk of stroke in the valsartan group, likely resulting from this same BP differential that favored amlodipine. The investigators highlighted the need for aggressive BP control in high-risk hypertensive patients, a goal that frequently requires combination therapy at the outset, a concept supported by the Blood Pressure Lowering Treatment Trialists' Collaboration.

1.1.3. ACE Inhibitors

ACE inhibitors should be prescribed to all CAD patients with stable angina who also have hypertension, diabetes

mellitus, an LV ejection fraction \leq 40%, or CKD unless contraindicated (Class I; Level of Evidence A). The clinical trials that support the use of ACE inhibitors in the management of patients with stable CAD were described in the Antihypertensive Drugs for the Secondary Prevention of Cardiovascular Events in Patients With CAD section. They are the HOPE study, in which high-risk individuals, 80% of whom had CAD, were given an ACE inhibitor (ramipril 10 mg/d), with a reduction in CVD end points by 20% to 25%; EUROPA, which showed a 20% relative risk reduction in the primary end point, a composite of cardiovascular death, MI, or cardiac arrest in patients in subjects with established CAD treated with perindopril 8mg/d versus placebo; and SAVE.

On the other hand, there have been negative studies. These include PEACE, in which patients with stable CAD and normal or slightly reduced LV function were randomized to trandolapril (target dose, 4 mg) or placebo. No difference between the groups was found in the incidence of the primary composite end point of cardiovascular death, MI, or coronary revascularization. Patients in the PEACE trial were at lower risk and were receiving more aggressive secondary prevention therapy than those in the HOPE trial. In ALLHAT, in which 25% of participants had CAD, there were no significant differences among patients taking chlorthalidone, amlodipine, and lisinopril in the combined outcomes of fatal CAD and nonfatal MI (the primary outcome of the study), in combined CAD (the primary outcome plus coronary revascularization or hospitalization for angina), or in all-cause mortality. Soon after the ALLHAT results were published, the Second Australian National Blood Pressure Study (ANBP-2) reported the results of a prospective, open-label study in patients 65 to 84 years of age with hypertension that showed, in men but not in women, better cardiovascular outcomes with ACE inhibitors than with diuretic agents despite similar reductions in BP.

1.1.4. Angiotensin Receptor Blockers

ARBs are recommended for all patients with stable angina who also have hypertension, diabetes mellitus, LV ejection fraction \leq 40%, or CKD and have indications for, but are intolerant of, ACE inhibitors (Class I; Level of Evidence A).

ARBs are indicated during hospitalization and at discharge for STEMI patients who are intolerant of ACE inhibitors and have HF or an ejection fraction $<$ 0.40 (Class I; Level of Evidence B). The combination of ACE inhibitors and ARBs has been used for the treatment of advanced or persistent HF in the convalescent or chronic phase after STEMI, but the ONTARGET Study failed to show additive benefit but with a substantial increase in side effects, so this combination is not recommended. In the VALUE trial, there was no difference in cardiac mortality and morbidity in patients with hypertension and high risk of cardiovascular events who were treated with regimens based on valsartan versus amlodipine, even though the BP-lowering effect of amlodipine was greater than that of valsartan. In VALIANT, valsartan was as no more effective than captopril in patients who were at high risk for cardiovascular events after MI.



1.1.5. Diuretics

Thiazide diuretics and thiazide-like diuretics reduce cardiovascular events, as demonstrated most convincingly in early studies such as the Veterans Administration studies, the MRC Trial, and SHEP and in later studies such as ALLHAT. These studies included subjects with CAD, and it is a reasonable assumption that diuretics are as effective in the secondary as in the primary prevention of cardiovascular events.

1.1.6. Nitrates

Long-acting nitrates or CCBs can be prescribed for the relief of symptoms when β -blockers are contraindicated or cause unacceptable side effects in patients with stable angina (Class I; Level of Evidence B). Long-acting nitrates or CCBs in combination with β -blockers should be prescribed for relief of symptoms when initial therapy with β -blockers is unsuccessful in patients with stable angina (Class I; Level of Evidence B). Nitrates should not be used with phosphodiesterase inhibitors of the sildenafil type. Hypertension does not affect the use of long-acting nitrates for the prevention of angina or of sublingual nitrate preparations for relief of an anginal attack. Conversely, nitrates have generally not been shown to be of use in the management of hypertension.

1.2. Recommendations

The management of symptomatic CAD, particularly angina pectoris, is directed to the relief of the angina and the prevention of both the progression of CAD and coronary events. The mainstays of angina treatment are β -blockers, CCBs, and nitrates. Pharmacological strategies for the prevention of cardiovascular events in these patients include ACE inhibitors, ARBs, thiazide and thiazide-like diuretics, β -blockers (particularly after MI), CCBs, antiplatelet drugs, and drugs for the treatment of dyslipidemia. The recent ACC Foundation/AHA guidelines recommend ACE inhibitors and/or β -blockers, with the addition of drugs such as thiazide diuretics or CCBs for the management of high BP in patients with stable IHD.

There are no special contraindications in hypertensive patients for the use of nitrates, antiplatelet or anticoagulant drugs, or lipid-lowering agents for the management of angina and the prevention of coronary events, except that in patients with uncontrolled severe hypertension who are taking antiplatelet or anticoagulant drugs, BP should be lowered without delay to reduce the risk of hemorrhagic stroke.

1. Patients with hypertension and chronic stable angina should be treated with a regimen that includes:

- (a) β -blocker in patients with a history of prior MI**
- (b) An ACE inhibitor or ARB if there is prior MI, LV systolic dysfunction, diabetes mellitus, or CKD; and**
- (c) A thiazide or thiazide-like diuretic (Class I; Level of Evidence A).**

2. The combination of a β -blocker, an ACE inhibitor or

ARB, and a thiazide or thiazide-like diuretic should also be considered in the absence of a prior MI, LV systolic dysfunction, diabetes mellitus, or proteinuric CKD (Class IIa; Level of Evidence B).

3. If β -blockers are contraindicated or produce intolerable side effects, a nondihydropyridine CCB (such as diltiazem or verapamil) may be substituted, but not if there is LV dysfunction (Class IIa; Level of Evidence B).

4. If either the angina or the hypertension remains uncontrolled, a long-acting dihydropyridine CCB can be added to the basic regimen of β -blocker, ACE inhibitor, and thiazide or thiazide-like diuretic. The combination of a β -blocker and either of the nondihydropyridine CCBs (diltiazem or verapamil) should be used with caution in patients with symptomatic CAD and hypertension because of the increased risk of significant bradyarrhythmias and HF (Class IIa; Level of Evidence B).

5. For patients with stable angina, the BP target is <140/90 mmHg. (Class I; Level of Evidence A). However, a lower target BP (<130/80 mmHg) may be considered in some individuals with CAD, with previous stroke or transient ischemic attack, or with CAD risk equivalents (carotid artery disease, PAD, abdominal aortic aneurysm) (Class IIb; Level of Evidence B).

6. There are no special contraindications in hypertensive patients for the use of antiplatelet or anticoagulant drugs, except that in patients with uncontrolled severe hypertension who are taking antiplatelet or anticoagulant drugs, the BP should be lowered without delay to reduce the risk of hemorrhagic stroke (Class IIa; Level of Evidence C).

2. Management of Hypertension in Patients With ACS

Although a major risk factor for CVD, the impact of hypertension on ACS outcomes has not been well described. Few data are available on specific treatments for hypertension in patients with either STEMI or non-ST-segment-elevation ACS, including both UA and NSTEMI.

2.1. Prevalence and Impact on Prognosis

Contemporary data from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry–Get With The Guidelines (GWTG) demonstrate a prevalence of hypertension of 65.2% among patients with STEMI and 79.2% among those with NSTEMI. The prevalence of hypertension increases notably with age among ACS patients, with hypertension prevalence rates approximately double among individuals >75 versus those <45 years of age.

In patients with stabilized ACS enrolled in the Sibrafiaban Versus Aspirin to Yield Maximum Protection From Ischemic

Heart Events Post-Acute Coronary Syndromes (SYMPHONY) trials, hypertension was an independent predictor of death and MI at 90 days. Moreover, hypertension is integrated into the Thrombolysis in Myocardial Infarction risk score for UA/NSTEMI as one of several classic risk factors for CAD, and the variable of ≥ 3 risk factors for CAD was independently associated with the composite end point of mortality and recurrent ischemic events. However, other multivariable risk models have not found hypertension, defined as a “yes/no” categorical variable, to be independently associated with in-hospital mortality. Indeed, lower BP more typically emerges as predictive of poor outcomes in contemporary evaluations. In both the Global Registry of Acute Coronary Events (GRACE) and ACTIONGWTG registries, for example, in-hospital mortality increased by $\approx 20\%$ for every 10-mmHg decrease in BP at presentation. In contrast to the Thrombolysis in Myocardial Infarction risk score for UA/NSTEMI, in the Thrombolysis in Myocardial Infarction risk score for STEMI, SBP < 100 mmHg emerged as a powerful contributor to the model, but hypertension did not.

Although uncontrolled hypertension does not appear to significantly increase in-hospital mortality in patients with ACS, it is a major risk factor for intracranial hemorrhage and thus remains a relative contraindication to fibrinolysis.

When broader bleeding outcomes are evaluated across the ACS spectrum, a U-shaped association between BP and in-hospital bleeding is observed, with excess bleeding for both patients with hypertension and those with hypotension. In an analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) Registry, bleeding rates were lowest in patients with admission SBP between 120 and 180 mmHg and increased progressively with BPs above and below these ranges. Similarly, in the NCDR ACTION Registry Bleeding Risk Score, zero points are awarded for an SBP of 141 to 170 mmHg on arrival, with 2 points given for SBP > 200 mmHg and 4 points for SBP ≤ 90 mmHg. In contrast, BP variables did not emerge as independently associated with bleeding in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) and Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials.

These studies have important limitations that make it difficult to determine the impact of treating hypertension during an acute ACS episode. All of the data are observational, and it is likely that residual confounding explains some, if not most, of the observed adverse association between lower BP and mortality after ACS, particularly for BP values within or near the normal range. In addition, very limited information is available from these studies on the duration of and long-term disease burden of hypertension. Despite these limitations, the consistent associations observed between hypotension and both mortality and bleeding suggest that avoidance of hypotension should be an important treatment principle in ACS patients.

5.2. General Principles of BP Management in the Patient With ACS

The cornerstone of the management of hypertension in patients with ACS is the modification of the balance between myocardial oxygen supply and demand. Patients with ACS are especially vulnerable to perturbations in this relationship because the development of an ACS is a clinical manifestation of an alteration in the supply-demand equation such that ischemia occurs at rest or at relatively low levels of demand. Although an elevated BP increases myocardial oxygen demand, rapid and excessive lowering of the DBP has the potential to result in impairment of coronary blood flow and oxygen supply. In addition, patients with ACS often have vasomotor instability with an increased tendency to exaggerated responses to antihypertensive therapy.

Because specific trials of BP lowering have not been performed in patients with ACS, the selection of antihypertensive agents for use in the patient with ACS should be focused on selecting drugs that have an established evidence-base for risk reduction for patients with ACS independently of BP lowering. These drugs, which include β -blockers, ACE inhibitors (or ARBs), and, in selected patients, aldosterone antagonists, should typically be titrated to full doses before other agents that do not have an established evidence base are initiated.

Therapeutic targets for BP have not been established specifically for patients with ACS. Current guidelines recommend a BP target of $< 140/90$ mmHg and $< 130/80$ mmHg for patients with diabetes mellitus or CKD, but this applies more to secondary prevention than the management of hypertension in the acute phase of MI. The BP may fluctuate early after ACS; thus, efforts should focus on pain control and clinical stabilization before BP is specifically targeted. Second, the BP should be lowered slowly, and caution is advised to avoid decreases in DBP to < 60 mmHg because this may reduce coronary perfusion and worsen ischemia. A BP target of $< 130/80$ mmHg at the time of hospital discharge is a reasonable option. In older hypertensive individuals with wide pulse pressures, lowering SBP may lead to very low DBP values, contributing to worsening myocardial ischemia.

2.3. Specific Antihypertensive Agents in ACS

2.3.1. Nitroglycerin

Nitroglycerin has been a cornerstone of therapy for decades, and in the hypertensive patient with ACS, nitroglycerin is effective in relieving symptoms of ischemia and pulmonary congestion and is moderately effective in lowering arterial BP. However, clinical trial evidence does not support an effect of nitrates on outcomes in ACS. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3 and International Study of Infarct Survival (ISIS)-4 trials included almost 80,000 patients with STEMI and found no difference in mortality with the use of nitrates (7.0% for those treated versus 7.2% who received placebo in GISSI-3; 7.3% versus 7.5%, respectively, in ISIS-4). Thus, the ACC/AHA guidelines for STEMI do not recommend



nitroglycerin to reduce events but only to relieve ischemic pain or acute hypertension or to manage pulmonary congestion at a Level of Evidence C. Nitrates should be used with caution in patients with inferior STEMI and are contraindicated if right ventricular infarction is present because of their effects on lowering preload. The guidelines caution that nitroglycerin should not be used at the expense of agents with proven benefits on outcomes such as β -blockers or ACE inhibitors (below), particularly in the convalescent stage.

Experience with nitrates in non-ST-segment-elevation ACS is largely extrapolated from STEMI because clinical trials in UA/NSTEMI have been relatively small. Nitroglycerin should be first administered via the sublingual route in patients with ACS, which can be followed by intravenous or topical administration of nitroglycerin or oral administration of longer-acting nitrate preparations. Patients treated with nitrates need to be monitored for potential adverse effects, in particular profound hypotension, which can exacerbate ischemia. Patients at increased risk include the elderly, individuals who are volume depleted, or those have used sildenafil within 24 hours or tadalafil within 48 hours. Nitrate tolerance is a problem even within the first 24 hours, and attempts should be made to minimize this by reducing intravenous doses and implementing intermittent dosing by nonintravenous routes once the patient is stable from an ischemic standpoint.

2.3.2. β -Blockers

β -Blockers are a cornerstone of ACS treatment because of their ability to reduce both heart rate and BP and thus myocardial oxygen demand. These agents were among the first therapies demonstrated to reduce infarct size. β -Blockers reduce early sudden death after MI both via antiarrhythmic effects and by preventing myocardial rupture. In patients with STEMI, the long-term benefits of long-term postdischarge β -blocker administration have been shown in multiple trials. Therefore, routine discharge use of β -blockers is now a quality performance measure for patients with ACS.

Although β -blockers should be initiated early and continued for at least 3 years after ACS, there has been increased attention on the appropriate selection of patients for the use of early intravenous β -blockers after ACS. Early intravenous β -blockade was shown in a number of trials performed in the fibrinolytic era to reduce either mortality or recurrent MI and thus was used as routine therapy in ACS for many years. However, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)/ Chinese Cardiac Study (CCC) 2 trial has led to a revision of the recommendations for intravenous β -blocker use in ACS. This study randomized 45,852 AMI patients at presentation to intravenous and then oral β -blockers versus placebo and assessed the coprimary outcomes of the composite of death, reinfarction, or cardiac arrest and death resulting from any cause. At discharge or up to 4 weeks, neither outcome was reduced with metoprolol. However, the COMMIT trial demonstrated a reduction in reinfarction (2.0% versus 2.5%) and ventricular

fibrillation (2.5% versus 3.0%), but at the expense of an increase in cardiogenic shock (5.0% versus 3.9%) with intravenous β -blocker use. The excess risk of shock was highest in the first 2 days of hospitalization, especially in patients with evidence of hemodynamic instability or borderline hemodynamics at presentation. In a subset analysis of patients with hypertension (SBP >140 mmHg), there were no statistically significant differences between the β -blocker and placebo arms with respect to the composite primary end point, death or cardiogenic shock alone, although there was a trend in favor of the β -blocker. This important study demonstrated that early intravenous β -blocker therapy should be used selectively and restricted to patients with significant hypertension or tachycardia (i.e., caused by atrial arrhythmias), those with ongoing ischemia, and those at low risk for hemodynamic compromise.

Current ACC/AHA guidelines for STEMI and UA/NSTEMI recommend that oral β -blockade should be started within the first 24 hours, once it is established that the patient is stable and there are no contraindications. The choice of a β -blocker is based on pharmacokinetic and side-effect criteria and physician familiarity, but in general, short-acting cardioselective (β_1 -selective) β -blockers without intrinsic sympathomimetic activity such as metoprolol or bisoprolol are preferable. Carvedilol, which also blocks β_2 and α_1 adrenergic receptors, has more potent BP-lowering effects than β_1 -selective agents and therefore may be a good choice for patients with ACS and severe hypertension. However, it should be avoided in patients with obstructive airways disease because of the effects of β_2 antagonism on airway resistance. Contraindications to the use of β -blockers in ACS include marked first-degree heart block (ECG PR interval >0.24 second), second- or third-degree heart block, severe bronchospastic lung disease, decompensated HF, and hypotension. Several meta-analyses concluded that cardioselective β -blockers do not produce clinically significant adverse respiratory effects in patients with chronic obstructive pulmonary disease, suggesting that β -blockers should not be withheld from these patients.

2.3.3. Calcium Channel Blockers

In general, CCBs have not been found to be useful in the setting of acute STEMI. Clinical trials of the rapid-release form of nifedipine showed an increase in mortality in patients treated with this agent after MI, and there is currently no role for short-acting nifedipine in clinical practice. The nondihydropyridine agents diltiazem and verapamil have also been disappointing in the early-MI setting and are not recommended for routine use in patients with STEMI.

Although several randomized, clinical trials suggested somewhat greater efficacy for CCBs in non-ST-segment-elevation ACS, some of these studies were performed \approx 30 years ago and predate the era of routine β -blocker use. Moreover, benefit in these trials was limited to nonfatal recurrent ischemic events, and among patients with LV dysfunction, a detrimental effect on mortality was seen. Thus, there is no indication for routine use of CCBs in patients with UA or NSTEMI. The AHA/ACC guidelines for



the management of UA and NSTEMI suggest that, in patients with continuing or frequently recurring ischemia when β -blockers are contraindicated, a nondihydropyridine CCB (verapamil or diltiazem) may be used as an alternative in the absence of severe LV dysfunction or other contraindications. It is prudent to avoid the use of verapamil or diltiazem in patients who have LV dysfunction, and they should not be used together with β -blockers in that situation. Evidence for the utility of dihydropyridine CCBs in ACS is limited. These agents effectively lower BP and may relieve ischemic symptoms. All CCBs have the potential to cause hypotension, and the nondihydropyridine CCBs may precipitate conduction disturbances, particularly when used in conjunction with β -blockers.

2.3.4. ACE Inhibitors

ACE inhibitors are indicated for most patients with ACS and are a preferred option for BP management in both STEMI and non-ST elevation ACS. The data are most robust for ACE inhibitors in the STEMI population, in whom most of the trials have been performed, with results extrapolated to UA/In STEMI, ACE inhibitors reduce infarct expansion, preventing LV remodeling and chamber dilatation, which help to prevent downstream sequelae such as ventricular arrhythmia, HF, or even myocardial rupture. The GISSI-3, ISIS-4, and CCS-1 trials demonstrated a benefit from early administration of ACE inhibitors, with absolute reductions in mortality of 0.8%, 0.5%, and 0.5% seen as early as 4 weeks after AMI.

A meta-analysis from the ACE Inhibitor Myocardial Infarction Collaborative Group, which included \approx 10,000 patients treated within 36 hours of acute MI, found a 7% lower relative mortality rate at 30 days in patients treated with ACE inhibitors. The benefit was largest in high-risk groups such as those with HF at presentation (23 lives saved per 1,000 patients) and those with an anterior MI (11 lives saved per 1,000 patients). Rates of nonfatal HF were also reduced, but hypotension and renal dysfunction were more common. When ACE inhibitors are started later after MI among individuals with LV dysfunction and continued long term, their benefits are even more robust; mortality rates have been reduced by \approx 20% to 25% in long-term trials evaluating ACE inhibitors in these high-risk subgroups.

2.3.5. Angiotensin Receptor Blockers

ARBs are a useful alternative to ACE inhibitors in patients with an ACE inhibitor contraindication or intolerance. The VALIANT trial randomized patients with LV dysfunction or HF within 10 days after acute MI to additional therapy with valsartan, captopril, or the combination of the two. Valsartan was as effective as captopril for reducing cardiovascular events in these high risk patients through 2 years of follow-up. However, combining valsartan with captopril increased the rate of adverse events without improving survival. On the other hand, OPTIMAAL showed a trend toward increased mortality in patients receiving losartan 50 mg once daily over patients receiving captopril 50 mg 3 times daily. These negative results may have been

attributable to inadequate dosing of losartan. In summary, because of the larger and more consistent evidence base for ACE inhibitors, these agents are preferred over ARBs for patients who can tolerate them, but ARBs are a first-line alternative for ACE inhibitor-intolerant patients.

2.3.6. Aldosterone Antagonists

Aldosterone, which is incompletely suppressed even among individuals on high doses of ACE inhibitors, is thought to contribute to both adverse ventricular remodeling and myocardial fibrosis after MI. The EPHESUS trial enrolled $>$ 6,600 patients with MI who had an LV ejection fraction \leq 40% and either signs of HF or diabetes mellitus. Patients were randomized to the selective aldosterone inhibitor eplerenone or placebo, initiated 3 to 14 days after MI. Eplerenone reduced total mortality by 15% and cardiovascular mortality by 17%, with a reduction in sudden cardiac death of 21%. Of those enrolled, 87% were receiving ACE inhibitors and 75% were receiving β -blockers, indicating that aldosterone antagonist therapy provides incremental benefit to these agents. Although spironolactone has not been studied specifically in ACS, this agent demonstrated a significant mortality benefit for patients with New York Heart Association (NYHA) class III or IV HF in the RALES trial, and it is also reasonable to use spironolactone for patients after ACS who meet EPHEUS criteria.

Aldosterone antagonists should be avoided in patients with significantly elevated serum creatinine levels (\geq 2.5 mg/dL in men, \geq 2.0 mg/dL in women) or elevated potassium levels (\geq 5.0 mEq/L) because there is a serious risk of hyperkalemia with the use of these agents in patients with an estimated creatinine clearance of $<$ 50 mL/min. Close clinical and laboratory follow-up is needed for patients receiving long-term treatment with aldosterone antagonists to mitigate the occurrence and complications of hyperkalemia.

Mineralocorticoid antagonists are underused among evidence-based medications after MI. This likely reflects appropriate concerns about the risk for hyperkalemia with these agents. However, many patients can safely receive these highly effective and inexpensive agents with careful follow-up.

2.3.7. Diuretics

Although thiazide and thiazide-type diuretics play a major role in the long-term control of BP, in ACS, diuretics are used primarily for patients with evidence of increased filling pressures, pulmonary venous congestion, or HF. Particular caution is needed with regard to hypokalemia, which may precipitate arrhythmias after ACS. Loop diuretics are preferred over thiazide and thiazide-type diuretics for patients with ACS who have HF (NYHA class III or IV) or for patients with CKD and an estimated glomerular filtration rate of $<$ 45 mL/min.

2.4. Safety of Anticoagulation in Patients With Uncontrolled Hypertension

ACS therapy includes several strategies that involve platelet inactivation and anticoagulation to reduce the risk of



thrombosis and poor clinical outcomes. The relative efficacy and safety of anticoagulant and antiplatelet therapy do not differ substantially in patients with STEMI, NSTEMI, or UA. In the ACS population, these drugs are most effective when given early. These therapies can lead to major bleeding complications, most commonly in the gastrointestinal tract and at the site of femoral access for percutaneous coronary interventions. Most concerning is that, in the setting of uncontrolled hypertension, the risk of hemorrhagic stroke is increased. This provides another rationale for the aggressive control of hypertension in patients with ACS.

Rapidly stabilizing patients to facilitate prompt coronary reperfusion is challenging in ACS patients with severe hypertension. Inherent to the use of medications largely limiting or disrupting intraluminal thrombus formation is the potential for severe secondary bleeding. The decision to pursue an invasive as opposed to a conservative approach should be based on standard clinical, demographic, and angiographic criteria. Although hypertension per se should not influence revascularization decisions other than indirectly in relation to factors such as renal function, it should be remembered that bleeding risks are notably higher with uncontrolled hypertension.

2.5. Conclusions

Hypertension will continue to be highly prevalent among patients with ACS, particularly as the ACS population ages. The majority will respond to standard methods of hypertension control. To control BP, specific agents should be selected that have an established evidence base for risk reduction in ACS. These agents include β -blockers, ACE inhibitors or ARBs, and, in selected patients, aldosterone antagonists. Although nitrates do not change the natural history of ACS, they are very useful for hypertensive patients with ACS, particularly if there is ongoing ischemia or pulmonary congestion. Particular care should be taken to avoid hypotension, with the risk of worsening myocardial ischemia. The benefits of treating hypertension in the ACS setting are logical, but perhaps the major impact on long-term morbidity and mortality depends on the efficacy of continued outpatient BP control once effective therapy has been initiated in hospital.

2.6. Recommendations

1. If there is no contraindication to the use of β -blockers, in patients with ACS, the initial therapy of hypertension should include a short-acting β_1 -selective β -blocker without intrinsic sympathomimetic activity (metoprolol tartrate or bisoprolol).

β -Blocker therapy should typically be initiated orally within 24 hours of presentation (Class I; Level of Evidence A). For patients with severe hypertension or ongoing ischemia, an intravenous β -blocker (esmolol) can be considered (Class IIa; Level of Evidence B). For hemodynamically unstable patients or when decompensated HF exists, the initiation of β -blocker therapy should be delayed until stabilization has been achieved (Class I; Level of Evidence A).

2. In patients with ACS and hypertension, nitrates should be considered to lower BP or to relieve ongoing ischemia or pulmonary congestion (Class I; Level of Evidence C). Nitrates should be avoided in patients with suspected right ventricular infarction and in those with hemodynamic instability. Sublingual or intravenous nitroglycerin is preferred for initial therapy and can be transitioned later to a longer-acting preparation if indicated.

3. If there is a contraindication to the use of a β -blocker or intolerable side effects, then a nondihydropyridine CCB such as verapamil or diltiazem may be substituted for patients with ongoing ischemia, provided that LV dysfunction or HF is not present. If the angina or hypertension is not controlled on a β -blocker alone, a longer-acting dihydropyridine CCB may be added after optimal use of an ACE inhibitor (Class IIa; Level of Evidence B).

4. An ACE inhibitor (Class I; Level of Evidence A) or an ARB (Class I; Level of Evidence B) should be added if the patient has an anterior MI, if hypertension persists, if the patient has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus. For low-risk ACS patients with preserved LV ejection fraction and no diabetes mellitus, ACE inhibitors can be considered a first-line agent for BP control (Class IIa; Level of Evidence A).

5. Aldosterone antagonists are indicated for patients who are already receiving β -blockers and ACE inhibitors after MI and have LV dysfunction and either HF (NYHA class III or IV) or for patients with CKD and an estimated glomerular filtration rate <30 mL/min. For patients with persistent hypertension not controlled with a β -blocker, an ACE inhibitor, and an aldosterone antagonist, a thiazide or thiazide-type diuretic may be added in selected patients for BP control (Class I; Level of Evidence B).

6. Loop diuretics are preferred over thiazide and thiazide-type diuretics for patients with ACS who have HF (NYHA class III or IV) or for patients with CKD and an estimated glomerular filtration rate <30 mL/min. For patients with persistent hypertension not controlled with a β -blocker, an ACE inhibitor, and an aldosterone antagonist, a thiazide or thiazide-type diuretic may be added in selected patients for BP control (Class I; Level of Evidence B).

7. The target BP is $<140/90$ mm Hg in patients with ACS who are hemodynamically stable (Class IIa; Level of Evidence C). A BP target of $<130/80$ mm Hg at the time of hospital discharge is a reasonable option (Class IIb; Level of Evidence C). The BP should be lowered slowly, and caution is advised to avoid decreases in DBP to <60 mm Hg because this may reduce coronary perfusion and worsen ischemia.

Ref.: Selected sections are extracted from "Treatment of Hypertension in Patients With Coronary Artery Disease", A Scientific Statement From the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation May 12, 2015.

Cardiology News

Working Long Hours Can Up Stroke, CHD Risk

Working 55 or more hours a week is associated with an increased risk for stroke, and the more hours put in at the office or other workplace the greater the increase in risk, a new meta-analysis shows. Long working hours were also associated with an increased risk for coronary heart disease (CHD), but the association was weaker than that for stroke. Compared with standard working hours (35 to 40 hours per week), working long hours, defined as 55 or more hours a week, raised the risk for stroke after adjustment for age, sex, and socioeconomic status.

August 20, *The Lancet*.

Visit-to-Visit Blood-Pressure Variability May Predict CV Risk

Hypertensive patients with significant changes in blood-pressure readings over several office visits had an increased risk of stroke, MI, heart failure, and death during a 2.8-year follow-up— independent of how well their hypertension was controlled. Until recently, variations in office blood-pressure readings over time were dismissed as random fluctuations. For patients with wide variations in visit-to-visit blood-pressure readings, clinicians can take a careful patient history to check medication adherence and diet, and they should ensure that blood pressure is being measured in a standard way after the patient has been resting at least 5 minutes.

Ann Intern Med 2015; DOI:10.7326/M14-2803

MESA: Impaired Fasting Glucose May Be a Risk Factor for Unrecognized MI

The prediabetes marker of impaired fasting glucose (IFG) may also be a predictor of silent MI in adult patients, suggests new research. Additional analysis from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that, among nearly 6,000 participants, those with IFG were significantly more likely to have an unrecognized MI than those with normal fasting glucose (adjusted odds ratio [OR] 1.60, 95% CI 1.0–2.5). The association was also significant for the men with IFG vs those without (fully adjusted OR 1.89, P=0.03), but not for the women. Unrecognized MI was determined in the study by whether a participant had pathological Q waves or minor Q waves with ST-T abnormalities on initial 12-lead ECG.

Am Heart J 2015; DOI:10.1016/j.ahj.2015.08.003.

Low-Normal Serum Sodium Identified as a Risk Factor for CVD/Death

More evidence has emerged that mild hyponatremia, even within the normal sodium range, as well as hypernatremia are both associated with increased risk of cardiovascular disease and mortality in older men with no history of coronary heart disease, heart failure, or stroke. In contrast to serum sodium, no consistent association was seen between potassium and overall CVD events.

Nutr Metab Cardiovasc Dis 2015

Editorial Board

Dr. Omar Akramur Rab, MBBS, FCGP, FIAGP
Kazi Md. Mizan, M. Pharm

Executive Editor

A.Z.M. Rashed
e-mail: azm-rashed@squaregroup.com

Anril[®]

Nitroglycerin

2.6 mg SR Tablet
0.5 mg SL Tablet
400 mcg/Spray
5 mg/ml IV Injection

*The classical
anti-anginal agent*

Nebita[™]

Nebivolol Hydrochloride Tablet

2.5 mg
5 mg

The 3rd generation β-blocker

Angilock[®]

Losartan Potassium Tablet

25 mg
50 mg
100 mg

*The trusted
Angiotensin Receptor Blocker*

Bisocor[®]

Bisoprolol Tablet

2.5 mg
5 mg
10 mg

The most selective β₁-blocker

Editorial Note

Dear Doctor,

We are happy to present the 38 issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue has selected portion from "Treatment of Hypertension in Patients With Coronary Artery Disease". We will appreciate your thoughtful comments. Thanks and regards.