Hypertension is a common disease which is increasing in incidence and prevalence across the world. Though common and easy to diagnose, it is disappointing to note that it remains under detected and under treated. In fact, only about 1/3rd of patients are optimally treated. Hypertension is one of the major risk factors for coronary artery disease (CAD), which can often be present in hypertensive patients. CAD is also increasing in magnitude in many geographical regions of the world including India. This clinical scenario poses a challenge as well as opportunity to the clinician. The optimal choice of antihypertensive agents remains controversial and there are only partial answers to important questions in the treatment of hypertension in the prevention and management of CAD. The areas of discussion in this write up will be, what is the appropriate BP target in CAD? Are there any drugs with effect beyond the blood pressure (BP) control? What should be the drugs we choose in patients with Stable CAD, Unstable angina (UA), NSTEMI and STEMI? The discussion shall be based on the best available data, trials etc and only where such data is not available personal opinions are expressed.

**Epidemiology of CAD in Hypertension:**

The relative importance of SBP and DBP as risk indicators changes with age. Below fifty years of age, DBP is the major predictor of IHD risk, whereas above sixty, SBP is more important. At all ages, the relationship between SBP or DBP and IHD mortality is consistent, robust, and continuous, with no apparent threshold value. In a meta-analysis of 61 studies that included almost 1 million adults, BP was related to fatal IHD over the range of 115/75 to 185/115 mm Hg. Overall, an increase of 20 mm Hg in SBP (or 10 mm Hg in DBP) doubles the risk of a fatal coronary event. Absolute risk of these adverse outcomes also increases with age, such that for any given SBP, the risk of fatal CAD was 16-fold higher for persons 80 to 89 years of age than for those 40 to 49 years of age. Further, there is a interrelationship between hypertension, dyslipidemia, glucose intolerance, cigarette smoking, and left ventricular (LV) hypertrophy. Besides, in patients with CAD presenting with various clinical syndromes there could be dynamic changes in BP which necessitates further fine tuning of choices of therapy. This brings out the fact that, in a given patient of CAD with hypertension many clinical issues need to be looked into not just the BP numbers.

**Effects of Treatment:**

The risk of CAD can be greatly reduced with effective antihypertensive therapy. The major reductions in cardiovascular morbidity and mortality over the past 50 years have been attributed mainly to the increased availability and utilization of various drug treatments for hypertension. Randomized trials have shown that BP lowering produces rapid reductions in cardiovascular risk that are highly consistent with predictions of risk reduction that can be inferred from observational studies. For example, a 10-mm Hg lower than usual SBP (or a 5-mm Hg lower than usual DBP) would predict a 50% to 60% lower risk of stroke death and an approximately 40% to 50% lower risk of death due to CAD or other vascular causes at middle age.

**Management of Hypertension in Patients with CAD and Stable Angina:**

Management of hypertension in patients with chronic CAD with 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. In an occasional patient, recognition and treatment of conditions like anemia, hypothyroidism and obstructive sleep apnea are important. Pharmacological management is inevitably required. A reasonable BP target for hypertensive patients with demonstrated CAD or with CAD risk equivalents is <130/80 mm Hg. However, it is important to note that too low a BP could be counterproductive producing not only symptoms of hypoperfusion or even worse cardiovascular outcomes, so called ‘j curve’ phenomenon. Existence of such a phenomenon though discussed it is controversial. It is reasonably intuitive to believe that treated lower pressures should bring about significant benefit to the population treated. But, detailed analyses have been inconclusive. In an individual patient it needs to be cautiously approached making sure that the symptoms of “low” pressures do not make him worse.

**Pharmacological Therapy:**

**β-Blockers**

β-Blockers are the drugs of first choice for the treatment of hypertension in patients with CAD and angina. The negative inotropic and chronotrophic actions of β-blockers...
make them ideal as the balance between the oxygen demand and supply of myocardium is abnormal nearly in all patients barring few patients. Balance is favorably altered by the beta blockers. Further, beta blockers also inhibit renin release. Cardioselective (β1) agents without intrinsic sympathomimetic activity are commonly used. Relative contraindications to their use include significant sinus or atrioventricular node dysfunction, hypotension, decompensated HF, and severe bronchospastic lung disease. In such situations it may become necessary to withdraw or reduce the beta blockers which might worsen the angina. Peripheral arterial rarely worsens with the use of these agents, and mild bronchospastic disease is not an absolute contraindication. 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 compelling data. The use of β-blockers for secondary prevention in all the lowest-risk patients is a Class I American College of Cardiology (ACC)/AHA recommendation (Level of Evidence A). Even for the lowest-risk patients, the weight of evidence and consensus opinion favor their use (Class IIa ACC/AHA recommendation, Level of Evidence B).

**Calcium Channel Blockers**

CCBs are added to, or substituted for, β-blockers when BP remains elevated, when angina persists, or when drug side effects or contraindications mandate. As a class, CCBs reduce myocardial oxygen demand by decreasing peripheral vascular resistance and lowering BP and increase myocardial oxygen supply by coronary vasodilation. Long-acting dihydropyridine agents are preferred over nondihydropyridines for use in combination with β-adrenoreceptor 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 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 inhibitortrandolapril 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, respectively. 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 diuretic, a long-acting dihydropyridine CCB, or an ACE inhibitor: CAMELOT compared amiodipine or enalapril to placebo in normotensive patients with CAD, ≈60% of whom had a history of hypertension. Although BP reduction was similar in the 2 active treatment groups, adverse cardiovascular events occurred less frequently in the amiodipine group than in the enalapril group. An intravascular ultrasound substudy showed progression of atherosclerosis in the placebo group (P<0.001), a trend toward progression in the enalapril group (P=0.08), no progression in the amiodipine group (P=0.31). Amiodipine may have pleiotropic effects beyond BP lowering that favor atherosclerotic plaque stabilization.

In VALUE trial, 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 amiodipine group, whereas the risk of new-onset diabetes mellitus was lower in the valsartan group. Of note, amiodipine was significantly more effective in reducing BPTer there was also a strong trend for an excess risk of stroke in the valsartan group, likely due to this same BP differential that favored amiodipine. 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.

**ACE Inhibitors**

The long-term use of ACE inhibitors in patients with CAD who also have diabetes mellitus and/or LV systolic dysfunction is a Class I ACC/AHA recommendation (Level of Evidence A). Their use is also particularly appropriate for CAD patients with hypertension. The HOPE study, in which high-risk individuals given an ACE inhibitor experienced a reduction in cardiovascular disease endpoints 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 treated with perindopril 8 mg/d versus placebo; and SAVE. On the other hand, there have been negative studies these include PEACE, ALLHAT, there were no significant differences among chlorothalidone, amiodipine, 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 all-cause mortality.

**Angiotensin Receptor Blockers**

ARBare 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 ACC/AHA recommendation, 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 (Class IIb ACC/AHA recommendation, Level of Evidence B). 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 amiodipine, even though the BP-lowering effect of amiodipine was greater than that of valsartan. In VALLANT, valsartan was as effective as captopril in patients who were at high risk for cardiovascular events after MI.
Diuretics
Thiazide diuretics reduce cardiovascular events, as demonstrated most convincingly in early studies, such as the Veterans Administration studies, the MRC Trial, and SHEP,14 in later studies, such as ALLHAT.15 These studies are discussed in greater detail in the previous section.

Nitrates
Long-acting nitrates are indicated for the treatment of angina not controlled with adequate doses of β-blockers and CCBs in combination with hydralazine in selected HF patients, with or without hypertension. Hypertension does not impact 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 not been shown to be of use in the management of hypertension.

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH ACUTE CORONARY SYNDROMES—UNSTABLE ANGINA AND NSTEMI:
There are few data on the impact of antihypertensive treatment on clinical outcomes in hypertensive patients presenting with the acute coronary syndromes.

Prevalence
In large, multinational, randomized trials in patients with NSTEMI, the overall prevalence of hypertension in STEMI was approximately 50% and ranged from 37-58%. Patients with hypertension had a much higher prevalence of other risk factors such as diabetes mellitus, hyperlipidemia, prior MI, prior stroke, a history of HF, and prior revascularization.

Impact on Prognosis
Hypertension is integrated into various risk scores as an adverse prognostic factor and is an independent predictor of the composite end point of mortality and recurrent ischemic events.16 In patients with stabilized acute coronary syndromes in the Sibrafiban versus aspirin to Yield Maximum Protection from ischemic Heart events postacute cOroNary syndromes (SYMPHONY) trials, hypertension was an independent predictor of death and MI at 90 days.17 In the large Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of glycoprotein IIb/IIIa inhibitors, hypertension was predictive of death and death due to MI on univariate but not on multivariate analyses. In the Global Use of Strategies To Open occluded coronary arteries (GUSTO IIb) and PURSUIT trials,18 A very low SBP (<91 mm Hg) was strongly associated with 48-hour and 30-day mortality, but surprisingly, there was little difference in mortality between patients who had a high SBP (141 mm Hg) and those with an SBP in the normal or prehypertensive range (121 to 140 mm Hg). The limitation of all of these studies is that the correlation between BP and prognosis is based on a clinical history of hypertension or baseline BP and do not provide an evaluation of the impact on prognosis of treating hypertension during an acute episode.

General Principles of Management
The cornerstone of the management of hypertension in patients with acute coronary syndromes is the modification of the balance between myocardial oxygen supply and demand, in addition to the initiation of anticoagulant and platelet inhibitor therapy.19 Patients with acute coronary syndromes are especially vulnerable. 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 acute coronary syndromes often have vasomotor instability, with an increased tendency to exaggerated responses to antihypertensive therapy.

Anti-Ischemic and Antihypertensive Therapies
Nitroglycerin
Nitroglycerin has been a cornerstone of therapy for decades, in the hypertensive patient, intravenous nitroglycerin is effective in the reduction of BP and symptoms. Clinical trials of nitrates in non–ST-elevation acute coronary syndromes have, however, been relatively small.

Patients need to be monitored for potential adverse effects, particularly profound hypotension. Patients at increased risk include the elderly, individuals who are volume depleted, and those who have used sildenafil within 24 hours. Nitrate tolerance is a problem and attempts should be made to minimize this by reducing intravenous dosing and implementing intermittent dosing by non intravenous routes once the patient is stable from an ischemic standpoint.

β-Blockers
β-Blockers are a rational choice based on their ability to reduce both heart rate and BP and thus, myocardial oxygen demand, but their widespread use was based more on logic than hard evidence, because their popularity antedated large trials.15 However, later trials have demonstrated the benefits of β-blockers in conjunction with nitrates in patients who have not previously taken β-blocker therapy, and others provide evidence to suggest that the addition of β-blockers is helpful in patients with persistent chest pain. In patients presenting with persistent pain, and in the absence of contraindications be started oral β-blockers when the patient is stable. The choice of a β-blocker is based on pharmacokinetic side effect criteria, as well as physician familiarity, but in general, cardioselective (β1-selective) blockers without intrinsic sympathomimetic activity are preferable. Examples are metoprolol and bisoprolol. If the patient is hemodynamically unstable, the initiation of β-blocker therapy should be delayed until stabilization of cardiogenic shock or HF has been achieved.

Contraindications to the use of β-blockers in acute coronary syndromes include first-degree heart block (electrocardiographic PR interval >0.24 second), second- or third-degree heart block, severe bronchospastic lung disease, and decompensated HF. Two recent meta-analyses
Concluded that cardioselective β-blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease, which suggests that β-blockers should not be withheld from these patients.

Calcium Channel Blockers
The AHA/ACC guidelines for the management of unstable angina and NSTEMI suggest that in patients with continuing or frequently recurring ischemia when β-blockers are contraindicated, a nondihydropyridine CCB (verapamil or diltiazem) can be used as initial therapy in the absence of severe LV dysfunction or other contraindications. There are several randomized clinical trials that show efficacy for CCBs in acute coronary syndromes. These show that these agents prevent or relieve symptoms and the related ischemia as well as β-blockers do. The largest of these trials is the DANish Verapamil Infarction Trial (DAVIT), which showed a trend in reducing the outcomes of death or nonfatal MI in 3447 patients with suspected acute coronary syndromes administered intravenous verapamil at admission and then orally for 1 week. In the Diltiazem Reinfarction Study (DRTS), 576 patients were treated with diltiazem or placebo 24 to 72 hours after the onset of non–Q-wave MI. There was a significant reduction in reinfarction and refractory angina at 14 days. Similar findings were reported in the Multicenter Diltiazem Post-Infarction Trial (MDPIT). Retrospective analyses of the DAVIT and MDPIT trials have concluded that the administration of verapamil or diltiazem to patients with suspected acute coronary syndromes who have LV dysfunction has an overall detrimental effect on mortality, although some studies have shown that verapamil and diltiazem may be safe in these patients. However, it is prudent to avoid the use of verapamil or diltiazem in patients who have LV dysfunction, and they should definitely not be used together with β-blockers in that situation. Long-acting dihydropyridine CCBs should be used; short-acting dihydropyridine CCBs such as nifedipine can cause severe hemodynamic instability and should never be used unless in combination with a β-blocker. All CCBs have the potential to cause hypotension and conduction disturbances, particularly when used in conjunction with β-blockers. The combination of a long-acting dihydropyridine CCB and β-blocker should be used with great caution in patients with significant LV dysfunction.

ACE Inhibitors and ARBs
An ACE inhibitor should be prescribed if hypertension persists, if the patient has evidence of LV dysfunction or HF, or if the patient has diabetes mellitus. Whether the drug is administered intravenously or orally will depend on the hemodynamic stability of the patient. ARBs can be used as an alternative in ACEI intolerant patients.

Diuretics
Although thiazide diuretics play a major role in the long-term control of BP, in the acute setting, diuretics are primarily used for patients with evidence of increased filling pressures, pulmonary venous congestion, or HF.

Adjunctive Therapy
The role of antithrombotic and antiplatelet therapy will not be discussed in the context of this statement. Such drugs are a pivotal aspect of therapy, and in the setting of uncontrolled hypertension, the risk of hemorrhagic stroke is increased. It is logical, however, for BP to be stable and controlled before any intervention is begun.

Acute Severe Hypertension and “Flash” Pulmonary Edema:
Such patients may have elevated biomarkers and fall under the rubric of a non–ST-elevation acute coronary syndrome. Initial therapy with intravenous nitroglycerin, furosemide, and a short-acting or intravenous ACE inhibitor is appropriate, followed by the addition of other drugs under tight control and monitoring. If tachycardia or ischemia is the predominant presentation, intravenous esmolol together with intravenous nitroglycerin is usually the first choice. BP lowering should be aggressive but requires close monitoring, particularly in the presence of ongoing ischemia or cerebral symptoms. Intravenous labetalol is helpful in some patients. Intravenous nitroprusside is used frequently, but the key is careful titration and monitoring to avoid hypotension. The risk of cyanide toxicity limits the long-term use of nitroprusside.

CONCLUSIONS
In 56,963 elderly patients with NSTEMI in the CRUSADE (Coronary Revascularization Ultrasound Angioplasty DEvice trial) Registry, the use of guidelines-recommended care was associated with improved in-hospital outcomes in patients treated invasively or conservatively. The frequency of hypertension was 61.8% in patients >65 years of age and approximately 75% in an older age group. Age had a relatively modest impact on the use of aspirin and β-blockers, but the use of antithrombotics and platelet inhibitors was considerably less in the elderly.

MANAGEMENT OF HYPERTENSION IN PATIENTS WITH CAD AND STEMI:
Although a major risk factor for cardiovascular disease, the impact of hypertension on STEMI outcomes is not well described. Thus, although acute treatment for STEMI may include many antihypertensive drugs, little has been published on the appropriate treatment of hypertension at the time of presentation with STEMI.

Prevalence and Prognostic Impact
As in the unstable angina/NSTEMI cohort described in the previous section, a history of hypertension has been found to increase the risk of mortality after STEMI. However, the prognostic significance of BP on presentation for STEMI is not well characterized. Although several prognostic scores for STEMI include BP, they most frequently describe low BP on presentation as a negative predictor of survival. Yet, because of the increased risk of intracranial hemorrhage in patients with uncontrolled hypertension at presentation, hypertension remains a relative contraindication to fibrinolysis for STEMI. Thus, both acute hypertension and hemorrhagic stroke are associated with an increased risk of adverse outcomes in the setting of acute coronary syndromes.

General Principles of Management
As in the case of unstable angina/NSTEMI, the cornerstone...
of the management of hypertension in patients with acute coronary syndromes is modification of the balance between myocardial oxygen supply and demand, in addition to the initiation of antithrombotic and platelet inhibitor therapy.

Anti-Ischemic and Antihypertensive Therapies

Nitroglycerin

Nitroglycerin has historically been the preferred choice for management of both ischemic discomfort in acute coronary syndromes and acute hypertension; however, the level of evidence for these practices is not high. 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 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, and 7.3% versus 7.5%, respectively, in ISIS-4). Thus, the ACC/AHA guidelines do not recommend the use of nitroglycerin to reduce events but only to relieve ischemic pain or acute hypertension, or to manage pulmonary congestion, at a “C” level of evidence. Furthermore, 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 (see below), particularly in the convalescent stage.

β-Blockers

As in the unstable angina/NSTEMI setting, β-blockers are a logical choice in an attempt to reduce heart rate, contractility, and thereby oxygen demand. Their benefits when initiated at discharge and continued long term have been shown in multiple trials, and early intravenous use of β-blockers was seen in the TIMI II-B study to reduce ischemic events versus later use. Early intravenous β-blockade was also supported in the ISIS-1 trial and by a meta-analysis of 30 trials in nearly 30,000 patients. The recent publication of the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial)/Chinese Cardiac Study (CCS)-2 provided additional insight into β-blocker strategies. The conclusion is that early intravenous β-blocker therapy is beneficial but should be reserved for low-risk patients delayed a few days until after patients with signs of HF or shock have been stabilized.

ACE Inhibitors

ACE inhibitors to be used in first twenty four hours. In the setting of STEMI, ischemic/infarcted muscle increases wall stress, which causes the myocardium to remodel and dilate, a process that begins at the time of initial ischemic insult. ACE inhibitors could reduce infarct expansion/remodeling and chamber dilatation, thereby preventing sequelae such as ventricular arrhythmia, failure, or rupture. The GISSI-3, ISIS-4, and CCS-1 trials demonstrated a benefit to early administration of ACE inhibitors, with absolute reductions in mortality of 0.8%, 0.5%, and 0.5%, respectively, seen as early as 4 weeks after AMI. This effect of early (within 24 hours) ACE inhibitor therapy is particularly pronounced in higher-risk patients: those with anterior or particularly large infarcts, previous infarction, HF, depressed LV ejection fraction (LVEF), and tachycardia.

Angiotensin Receptor Blockers

ARBs are a useful alternative to ACE inhibitors. The VALIANT trial and OPTIMAAL trial have shown differing results.

Aldosterone Antagonists

Both spironolactone and eplerenone lower BP. These agents had secondary protective effect in patients with severe HF in the RALES study and in patients with LV dysfunction (LVEF≤40%) after MI in the EPHESUS. In the EPHESUS trial, there was a 15% reduction in mortality with eplerenone at 16 months. A reduction in mortality was seen as early as 30 days, which emphasizes the benefit of early inhibition of the RAAS and the clinical need to start therapy before discharge. However, aldosterone antagonists should be avoided in patients with elevated serum creatinine levels (≥2.5 mg/dL in men, ≥2.0 mg/dL in women) or elevated potassium levels (≥5.0 mEq/L), because there is a serious risk of hyperkalemia with use of these agents in patients with an estimated creatinine clearance of <50 mL/min.

Calcium Channel Blockers

In general, CCBs have not been found to be useful in the setting of acute STEMI. The nondihydropyridine agents diltiazem and verapamil have also been disappointing in the early-MI setting and are not recommended for patients with STEMI. However, no harm was observed in 1 study with verapamil in patients with HF after an acute MI, all of whom were treated with ACE inhibitors. Long-acting dihydropyridine CCBs are preferred after an acute MI for patients with continuing ischemic discomfort or rapid ventricular arrhythmias who are unresponsive to β-blockers or in whom β-blockers are contraindicated. Nondihydropyridine CCBs (diltiazem and verapamil) should be avoided in patients with modest to severe HF or bradyarrhythmias.

Diuretics

Although diuretics have a major role in the treatment of chronic hypertension and exacerbations of acute HF, their use is not supported in the acute STEMI setting.

Hypertension will continue to be a highly prevalent disease in populations with chronic Coronary artery disease and acute coronary syndromes, many of whom may be elderly. Nonetheless, the majority will respond to standard methods of hypertension control. The benefits of treating hypertension in the acute coronary syndrome 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 the hospital. β-blockers and ACEIs are mainstay of treatment of hypertension in all presentations of CAD. CCBs play an important role when β-blockers are contraindicated, not tolerated or inadequate. Though nitrates and diuretics have role in management of acute coronary syndrome patients, their role on long-term management is limited. Role of ARBs is emerging but limited to ACEI intolerant patients at present.

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